METHOD OF USING A CYCLOOXYGENASE-2 INHIBITOR AND SEX STEROIDS AS A COMBINATION THERAPY FOR THE TREATMENT AND PREVENTION OF DYSMENORRHEA

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to methods for the treatment and prevention of dysmenorrhea in a woman using a combination of a cyclooxygenase-2 inhibitor and sex steroids.

Description of the Related Art

In women, the menstrual cycle involves a complex series of hormonal changes. A consequence of these hormonal changes is the growth of the uterine lining (referred to as the endometrium). In the absence of pregnancy, the endometrium is shed in a process called menstruation. This process involves the release of prostaglandins, which cause contractions of the smooth muscle in the uterus. In some women, these contractions cause substantial pain, dysmenorrhea, which interferes with their daily activities.

The time at which menstruation occurs varies in that it can not be predicted with certainty in any one woman. The variability in the onset of menstrual cycles is dependent upon many variables including the individual woman, her age and underlying medical and psychosocial conditions. This makes it difficult to predict the onset of menses. Non-steroidal anti-inflammatory agents (NSAIDs) that inhibit prostaglandin synthesis are effective in reducing dysmenorrhea (Lundstrom, V., et al. Acta Obstet. Gynecol. Scand. Suppl., 113, 83-85 (1983)). They are most effective when administered prior to the onset of menstrual pain by 24-48 hours. Since predicting the precise timing of

menstruation is difficult, attempts to maximize efficacy by initiating treatment prior to menses may result in several days of unnecessary medication.

The use of orally active contraceptives, composed of estrogen and progestin components, has been reported to reduce the intensity of the pain of dysmenorrhea (Nabrink, M. et al. Contraception, 42, 275-283 (1990)). The vast majority of oral contraceptives consist of a combination of a progestin sex steroid and an estrogen sex steroid. These sex steroids are administered concurrently for 21 days followed by either a 7 day pill free interval or by the administration of a placebo for 7 days in each 28 day cycle. Numerous regimens have been developed in which the progestin/estrogen combination is administered either as a fixed dosage combination (monophasic) or as a biphasic or a triphasic regimen in which the dosage of the combination is varied either once or twice throughout the menstrual cycle. Kuhl has reviewed the current state of hormonal contraception (Handb. Exp. Pharmacol., 135/II, 363-407 (1999)). Various oral contraceptive combinations are listed in WO 98/04265. Most current oral contraceptives give good menstrual cycle control (Thorneycroft, I. Am. J. Obstet. Gynecol., 180 (2, Pt. 2), S280-S287 (1999)).

When good relief of dysmenorrhea is not obtained through the use of oral contraceptives, a nonsteroidal anti-inflammatory drug can be added as treatment (Deligeoroglou, E. Annals of the New York Academy of Science, 900, 237-244 (2000)).

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG2, PGH2 and PGE2, has been a common target of anti-inflammatory drug discovery. However, common non-steroidal anti-inflammatory drugs (NSAIDs) that are active in reducing

the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life-threatening ulcers, which limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long-term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase II (COX II)" or "prostaglandin G/H synthase II") provides a viable target of inhibition that more effectively reduces inflammation and produces fewer and less drastic side effects.

U.S. Patent No. 5,466,823 discloses pyrazolyl cyclooxygenase-2 inhibitors useful in treating inflammation and inflammation-related disorders, including menstrual cramps.

U.S. Patent No. 5,932,598 discloses prodrugs of cyclooxygenase-2 inhibitors useful in treating inflammation and inflammation-related disorders, including menstrual cramps.

Morrison et al. describe a study where the cyclooxygenase-2 inhibitor, rofecoxib, is used to treat primary dysmenorrhea (Obstet. Gynecol., 94(4), 504-508 (1999)).

Compounds that selectively inhibit cyclooxygenase-2 and are useful in treating menstrual cramps have also been described in the following individual publications.

U.S. Patent No. 5,521,207.

U.S. Patent No. 5,633,272.

The various classes of compounds that are selective inhibitors of cyclooxygenase-2 have been reviewed by J. Talley in Prog. Med. Chem., 36, 201-234 (1999). Compounds that selectively inhibit cyclooxygenase-2 have also been described in the following individual publications.

U.S. Patent No. 5,380,738.

U.S. Patent No. 5,344,991.

U.S. Patent No. 5,393,790.

U.S. Patent No. 5,434,178.

U.S. Patent No. 5,474,995.

U.S. Patent No. 5,510,368.

WO 96/06840.

WO 96/03388.

WO 96/03387.

WO 96/19469.

WO 96/25405.

WO 95/15316.

WO 94/15932.

WO 94/27980.

WO 95/00501.

WO 94/13635.

WO 94/20480.

WO 94/26731.

The combination of NSAIDs and oral contraceptives has been used in cases where neither treatment alone was effective in treating primary dysmenorrhea (Coco, A., American Family Physician, 60(2), 489-496 (1999)).

U.S. Patent No. 5,811,416 discloses the combination of an endothelin antagonist and/or an endothelin synthase inhibitor with at least one of a progestin, an estrogen, a combination of a progestin and estrogen, a cyclooxygenase inhibitor, a nitric oxide donor or a

nitric oxide substrate for the treatment of menstrual disorders including dysmenorrhea.

U.S. Patent No. 5,912,006 discloses the combination of an omega fatty acid and a cyclooxygenase inhibitor for the reduction or alleviation of uterine or vaginal pain associated with the onset of menstruation.

However, a combination therapy method for the treatment and prevention of dysmenorrhea comprising a COX-2 inhibitor and sex steroids has not been previously described.

BRIEF SUMMARY OF THE INVENTION

To address the continuing need to find safe and effective agents for the prophylaxis and treatment of dysmenorrhea, combination therapies of therapeutic agents are now reported.

Among its several embodiments, the present invention provides a therapeutic combination of a cyclooxygenase-2 inhibitor compound source and an amount of sex steroid compounds, wherein the compounds together comprise a dysmenorrhea-effective amount of the compounds.

In another embodiment, the cyclooxygenase-2 inhibitor compound source is a cyclooxygenase-2 inhibitor compound.

In yet another embodiment, the present invention provides a combination therapy method for the treatment or prophylaxis of dysmenorrhea in a patient in need thereof comprising the use of an amount of a cyclooxygenase-2 inhibitor compound and an amount of a sex steroid, wherein the amounts of the cyclooxygenase-2 inhibitor compound and the sex steroid compound together comprise a dysmenorrhea-effective amount of the compounds.

The invention involves the preventive management of painful uterine cramps, dysmenorrhea, in women. A key improvement over existing technologies is that moderate to severe pain is not experienced prior to initiating treatment, but that it can be preempted, providing a much more satisfactory outcome. Another advantage is that by employing this regimen, lower doses of analgesic medication may be required. There should also be an advantage of a reduced blood loss compared with existing treatments.

Further scope of the applicability of the present invention will become apparent from the detailed description provided below. However, it should be understood that the following detailed description and examples, while indicating preferred embodiments of the invention, are given by way of illustration only since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

The following detailed description is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be construed to unduly limit the present invention as modifications and variations in the embodiments discussed herein can be made by those of ordinary skill in the art without departing from the spirit or scope of the present inventive discovery.

The contents of each of the references cited herein, including the contents of the references cited within these primary references, are herein incorporated by reference in their entirety.

Definitions

The following definitions are provided in order to aid the reader in understanding the detailed description of the present invention.

The phrase "cyclooxygenase-2 inhibitor" or "COX-2 inhibitor" or "cyclooxygenase-II inhibitor" includes agents that specifically inhibit a class of enzymes, cyclooxygenase-2, with less significant inhibition of cyclooxygenase-1.

Preferably, it includes compounds that have a cyclooxygenase-2 IC_{50} of less than about 0.2 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 10 μM.

The phrase "sex steroids" includes both estrogen and progestin steroid compounds.

The phrase "combination therapy" (or "co-therapy") embraces the administration of a cyclooxygenase-2 inhibitor and a sex steroid as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). "Combination therapy" generally is not intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that

incidentally and arbitrarily result in the combinations of the present invention. "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical. "Combination therapy" also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies.

The phrase "therapeutically effective" is intended to qualify the combined amount of inhibitors in the combination therapy. This combined amount will achieve the goal of reducing or eliminating dysmenorrhea.

"Therapeutic compound" means a compound useful in the prophylaxis or treatment of dysmenorrhea.

The term "comprising" means "including the following elements but not excluding others."

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms.
Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl.

The term "alkynyl" denotes linear or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon

atoms. Examples of such radicals include propargyl, butynyl, and the like.

The terms "alkenyl", "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "cycloalkyl" embraces saturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkenyl" embraces partially unsaturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having one to six carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

The terms "alkoxy" and "alkyloxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy,

aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

The term "heterocyclo" embraces saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclo radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclo radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

The term "heteroaryl" embraces unsaturated heterocyclo radicals. Examples of unsaturated heterocyclo radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclo group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for

example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclo group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic: group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclo group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also embraces radicals where heterocyclo radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, benzopyran, and the like. The terms benzopyran and chromene are interchangeable. Said "heterocyclo group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkyl" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about

ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl.

The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals.

The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denote NH_2O_2S-.

The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl.

The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes -(C=O)-. The term "aroyl" embraces aryl radicals with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The term "carboxyalkyl" embraces alkyl radicals substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which embrace lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl portions having 1 to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The terms benzyl and phenylmethyl are interchangeable.

The term "heterocycloalkyl" embraces saturated and partially unsaturated heterocyclo-substituted alkyl radicals, such as pyrrolidinylmethyl, and heteroarylsubstituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

The term "aralkoxy" embraces aralkyl radicals attached through an oxygen atom to other radicals. The term "aralkoxyalkyl" embraces aralkoxy radicals attached through an oxygen atom to an alkyl radical. The term "aralkylthio" embraces aralkyl radicals attached to a sulfur atom. The term "aralkylthioalkyl" embraces aralkylthio radicals attached through a sulfur atom to an alkyl radical.

The term "aminoalkyl" embraces alkyl radicals substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like. The term "alkylamino" denotes amino groups that have been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups that have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" embraces aralkyl radicals attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-

aryl-N-alkylaminoalkyl" denote amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl.

The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$. The term "alkylaminocarbonyl" denotes an aminocarbonyl group that has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" and "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above. The term "aminocarbonylalkyl" denotes a carbonylalkyl group that has been substituted with an amino radical on the carbonyl carbon atom.

The term "alkylaminoalkyl" embraces radicals having one or more alkyl radicals attached to an aminoalkyl radical. The term "aryloxyalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent oxygen atom. The term "arylthioalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

Combinations

The methods and combinations of the present invention provide one or more benefits. Combinations of COX-2 inhibitors with the compounds, compositions, agents and therapies of the present invention are useful in treating and preventing dysmenorrhea. Preferably, the COX-2 inhibitors and the compounds, compositions, agents and therapies of the present invention are administered in combination at a low dose, that is, at a dose lower

than has been conventionally used in clinical situations.

The combinations of the present invention will have a number of uses. For example, through dosage adjustment and medical monitoring, the individual dosages of the therapeutic compounds used in the combinations of the present invention will be lower than are typical for dosages of the therapeutic compounds when used in monotherapy. The dosage lowering will provide advantages including reduction of side effects of the individual therapeutic compounds when compared to the monotherapy. In addition, fewer side effects of the combination therapy compared with the monotherapies will lead to greater patient compliance with therapy regimens.

Alternatively, the methods and combination of the present invention can also maximize the therapeutic effect at higher doses.

When administered as a combination, the therapeutic agents can be formulated as separate compositions that are given at the same time or different times, or the therapeutic agents can be given as a single composition.

This new method of treatment for moderate to severe dysmenorrhea is superior to existing therapies, by reason of having the following characteristics. It inhibits the increased prostaglandin production induced by the complex series of hormonal changes characteristic of the menstrual cycle. The inhibition of prostaglandin synthesis occurs reproducibly 24-48 hours prior to initiation of menstruation. For safety reasons, it targets only the increased prostaglandin synthesis, which occurs immediately prior to menses, and not constitutive prostaglandin synthesis that may negatively impact other processes such as renal function.

The COX-2 enzyme, which is responsible for prostaglandin synthesis, has been demonstrated in the endometrium and myometrium of the uterus in women. The tissue distribution of COX-2 is significantly different from COX-1 in the endometrium. Therefore one would expect differences in the effects of COX-2 inhibitors compared to COX-1 inhibitors.

Among its several embodiments, the present invention provides a therapeutic combination of a cyclooxygenase-2 inhibitor compound source and a sex steroid compound, wherein the compounds together comprise a dysmenorrhea-effective amount of the compounds.

In another embodiment, the cyclooxygenase-2 inhibitor compound source is a cyclooxygenase-2 inhibitor compound.

In yet another embodiment, the cyclooxygenase-2 inhibitor compound source is a prodrug of a COX-2 inhibitor.

Nonlimiting examples of COX-2 inhibitors that may be used in the present invention are identified in Table 1 below.

Table No. 1. Cyclooxygenase-2 Inhibitors

Compound	Trade/ Research Name	Reference	Dosage
1,5-Diphenyl-3-substituted pyrazoles		WO 97/13755	
	radicicol	WO 96/25928. Kwon et al (Cancer Res (1992)	

		52 6296)	
	GB-02283745		
	TP-72	Cancer Res 1998 58 4 717 -723	
1-(4-chlorobenzoyl)-3-[4-(4-fluoro-phenyl)thiazol-2-ylmethyl]-5-methoxy-2-methylindole	A-183827.0		
	GR-253035		
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	JTE-522	JP 9052882	
5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl)-pyridine			
2-(3,5-difluoro-phenyl)-3-4-(methylsulfonyl)-phenyl)-2-cyclopenten-1-one			
	L-768277		
	L-783003		
	MK-966; VIOXX®	US 5968974	12.5-100 mg po
indomethacin-derived indolalkanoic acid		WO 96/374679	200 mg/kg/day
1-Methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene		WO 95/30656. WO 95/30652. WO 96/38418. WO	

		96/38442.	
4,4-dimethyl-2-phenyl-3-[4-(methylsulfonyl)phenyl]cyclo-butenone			
2-(4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole		EP 799823	
N-[5-(4-fluoro)phenoxy]thiophene-2-methanesulfon-amide	RWJ-63556		
5(E)-(3,5-di-tert-butyl-4-hydroxy)benzylidene-2-ethyl-1,2-isothiazolidine-1,1-dioxide	S-2474	EP 595546	
3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-benzopyran-4-one	T-614	DE 38/34204	
Benzenesulfonamide, 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-	celecoxib	US 5466823	
CS 502	(Sankyo)		
MK 633	(Merck)		
	meloxicam	US 4233299	15-30 mg/day
	nimesulide	US 3840597	

The following references listed in Table No. 2 below, hereby individually incorporated by reference, describe various COX-2 inhibitors suitable for use in the present invention described herein, and processes for their manufacture.

Table No. 2. COX-2 Inhibitor References

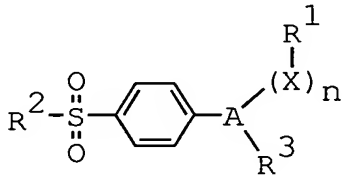
WO 99/30721	WO 99/30729	US 5760068	WO 98/15528
WO 99/25695	WO 99/24404	WO 99/23087	FR 27/71005
EP 921119	FR 27/70131	WO 99/18960	WO 99/15505
WO 99/15503	WO 99/14205	WO 99/14195	WO 99/14194
WO 99/13799	GB 23/30833	US 5859036	WO 99/12930
WO 99/11605	WO 99/10332	WO 99/10331	WO 99/09988
US 5869524	WO 99/05104	US 5859257	WO 98/47890
WO 98/47871	US 5830911	US 5824699	WO 98/45294
WO 98/43966	WO 98/41511	WO 98/41864	WO 98/41516
WO 98/37235	EP 86/3134	JP 10/175861	US 5776967
WO 98/29382	WO 98/25896	ZA 97/04806	EP 84/6,689
WO 98/21195	GB 23/19772	WO 98/11080	WO 98/06715
WO 98/06708	WO 98/07425	WO 98/04527	WO 98/03484
FR 27/51966	WO 97/38986	WO 97/46524	WO 97/44027
WO 97/34882	US 5681842	WO 97/37984	US 5686460
WO 97/36863	WO 97/40012	WO 97/36497	WO 97/29776
WO 97/29775	WO 97/29774	WO 97/28121	WO 97/28120
WO 97/27181	WO 95/11883	WO 97/14691	WO 97/13755
WO 97/13755	CA 21/80624	WO 97/11701	WO 96/41645
WO 96/41626	WO 96/41625	WO 96/38418	WO 96/37467
WO 96/37469	WO 96/36623	WO 96/36617	WO 96/31509
WO 96/25405	WO 96/24584	WO 96/23786	WO 96/19469
WO 96/16934	WO 96/13483	WO 96/03385	US 5510368
WO 96/09304	WO 96/06840	WO 96/06840	WO 96/03387
WO 95/21817	GB 22/83745	WO 94/27980	WO 94/26731
WO 94/20480	WO 94/13635	FR 27/70,131	US 5859036
WO 99/01131	WO 99/01455	WO 99/01452	WO 99/01130
WO 98/57966	WO 98/53814	WO 98/53818	WO 98/53817
WO 98/47890	US 5830911	US 5776967	WO 98/22101
DE 19/753463	WO 98/21195	WO 98/16227	US 5733909
WO 98/05639	WO 97/44028	WO 97/44027	WO 97/40012
WO 97/38986	US 5677318	WO 97/34882	WO 97/16435
WO 97/03678	WO 97/03667	WO 96/36623	WO 96/31509
WO 96/25928	WO 96/06840	WO 96/21667	WO 96/19469

Table No. 2. COX-2 Inhibitor References

US 5510368	WO 96/09304	GB 22/83745	WO 96/03392
WO 94/25431	WO 94/20480	WO 94/13635	JP 09052882
GB 22/94879	WO 95/15316	WO 95/15315	WO 96/03388
WO 96/24585	US 5344991	WO 95/00501	US 5968974
US 5945539	US 5994381		

Three classes of cyclooxygenase-2 inhibitors are reviewed by J. Carter in Exp. Opin. Ther. Patents, 8(1), 21-29 (1997): methanesulfonanilides, tricyclics and structurally modified non-selective cyclooxygenase inhibitors. Methanesulfonanilides are a class of selective cyclooxygenase-2 inhibitors, of which NS-398, flosulide and nimesulide are example members.

A preferred class of tricyclic cyclooxygenase-2 inhibitors comprises compounds of formula (1)



(1)

wherein A is a substituent selected from partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

wherein n is 0 or 1;

wherein X is O or S;

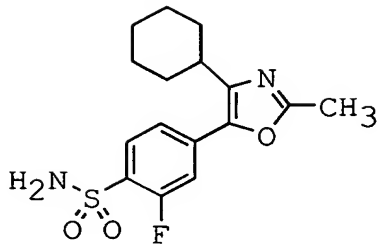
wherein R^1 is at least one substituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

wherein R^2 is methyl, amino or aminocarbonylalkyl; and

wherein R^3 is one or more radicals selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl and N-alkyl-N-arylaminosulfonyl, wherein R^3 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio; or a pharmaceutically-acceptable salt thereof.

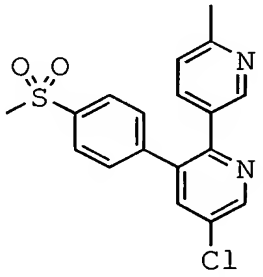
Preferred COX-2 inhibitors are tricyclic COX-2 inhibitors wherein the A ring is selected from the heterocyclyl groups of pyrazolyl, furanonyl, isoxazolyl, pyridinyl and pyridazinonyl.

More preferred COX-2 inhibitors that may be used in the present invention include, but are not limited to:



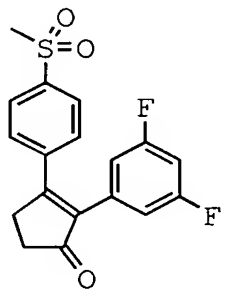
(C1)

JTE-522, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide;



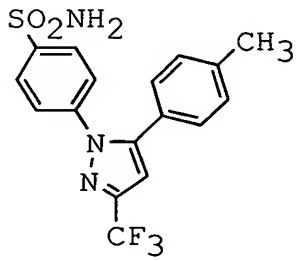
(C2)

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(2-methyl-5-pyridinyl)pyridine;



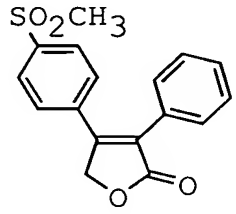
(C3)

2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one;



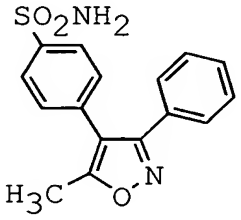
(C4)

celecoxib, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide;



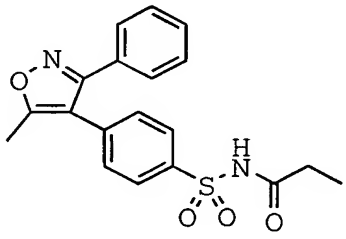
(C5)

rofecoxib, 4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone;



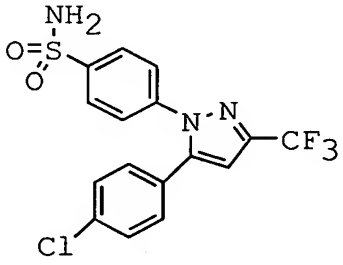
(C6)

valdecoxib, 4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;



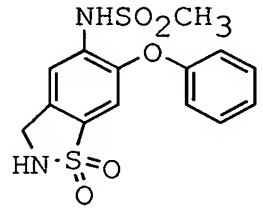
(C7)

parecoxib, N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;



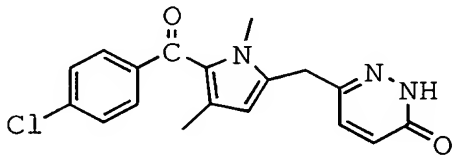
(C8)

4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide;



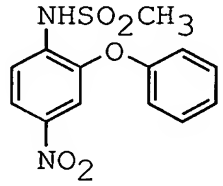
(C9)

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide;



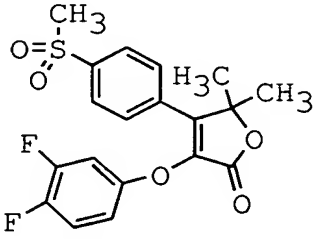
(C10)

6-[[5-(4-chlorobenzoyl)-1,4—dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone;



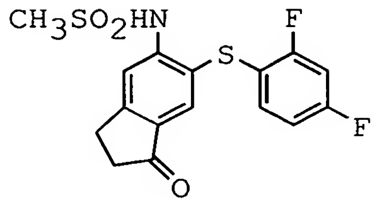
(C11)

N-(4-nitro-2-phenoxyphenyl)methanesulfonamide;



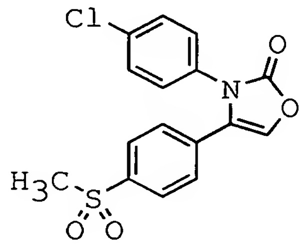
(C12)

3-(3,4-difluorophenoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-2(5H)-furanone;



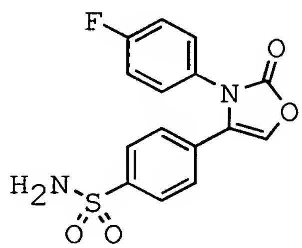
(C13)

N-[6-[(2,4-difluorophenyl)thio]-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide;



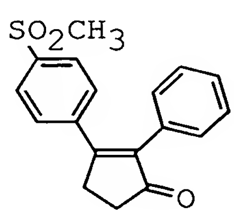
(C14)

3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone;



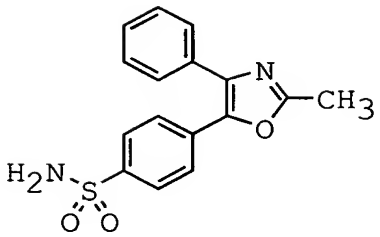
(C15)

4-[3-(4-fluorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide;



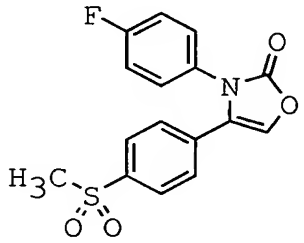
(C16)

3-[4-(methylsulfonyl)phenyl]-2-phenyl-2-cyclopenten-1-one;



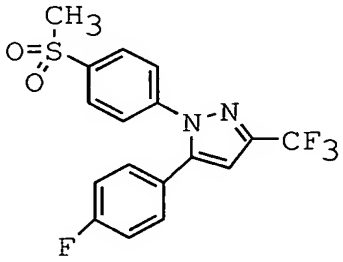
(C17)

4-(2-methyl-4-phenyl-5-oxazolyl)benzenesulfonamide;



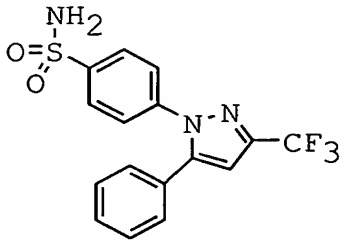
(C18)

3-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2(3H)-oxazolone;



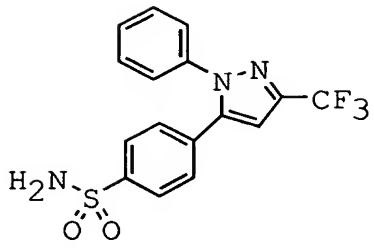
(C19)

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazole;



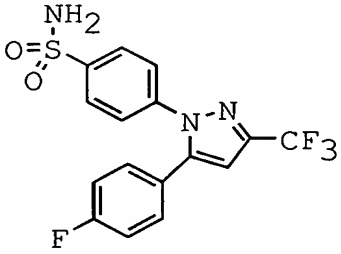
(C20)

4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;



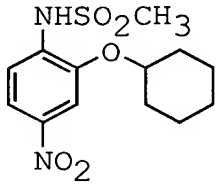
(C21)

4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzenesulfonamide;



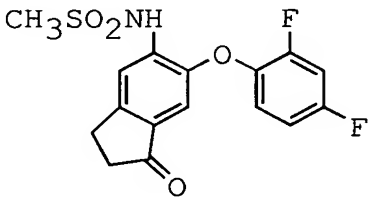
(C22)

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;



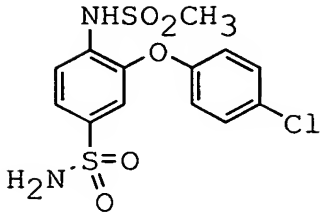
(C23)

NS-398, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide;



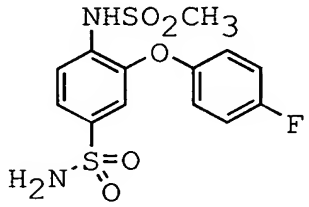
(C24)

N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]methanesulfonamide;



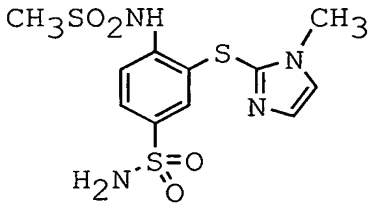
(C25)

3-(4-chlorophenoxy)-4-
[(methylsulfonyl)amino]benzenesulfonamide;



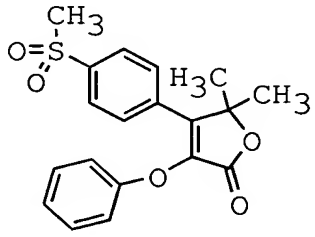
(C26)

3-(4-fluorophenoxy)-4-
[(methylsulfonyl)amino]benzenesulfonamide;



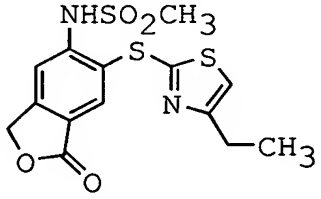
(C27)

3-[(1-methyl-1H-imidazol-2-yl)thio]-4
[(methylsulfonyl) amino]benzenesulfonamide;



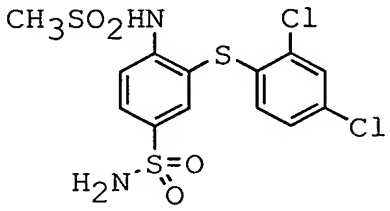
(C28)

5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-3-
phenoxy-2(5H)-furanone;



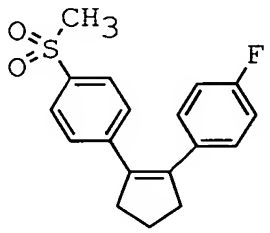
(C29)

N-[6-[(4-ethyl-2-thiazolyl)thio]-1,3-dihydro-1-oxo-5-isobenzofuranyl]methanesulfonamide;



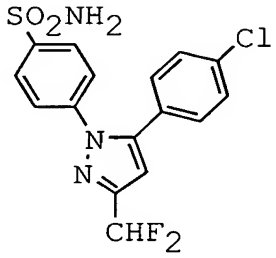
(C30)

3-[(2,4-dichlorophenyl)thio]-4-[(methylsulfonyl)amino]benzenesulfonamide;



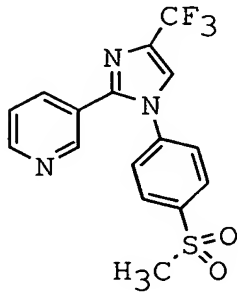
(C31)

1-fluoro-4-[2-[4-(methylsulfonyl)phenyl]cyclopenten-1-yl]benzene;



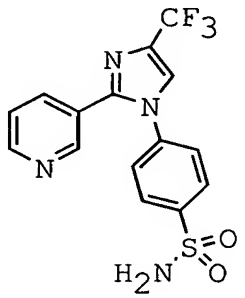
(C32)

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;



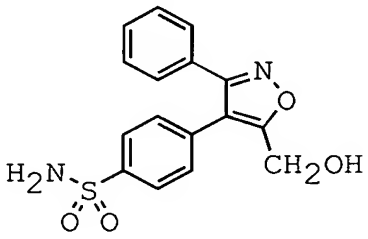
(C33)

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;



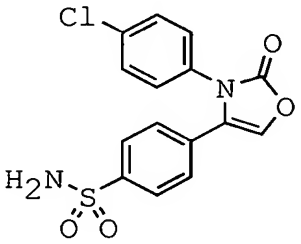
(C34)

4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;



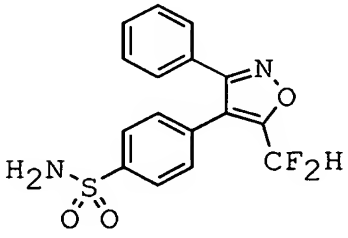
(C35)

4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;



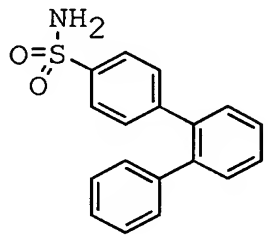
(C36)

4-[3-(4-chlorophenyl)-2,3-dihydro-2-oxo-4-oxazolyl]benzenesulfonamide;



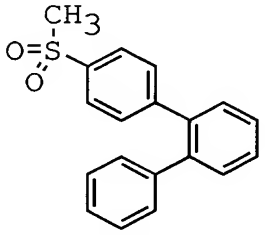
(C37)

4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]benzenesulfonamide;



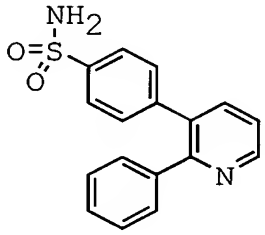
(C38)

[1,1':2',1"-terphenyl]-4-sulfonamide;



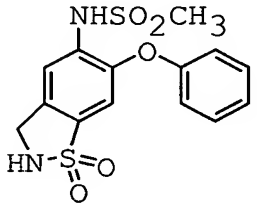
(C39)

4-(methylsulfonyl)-1,1',2],1"-terphenyl;



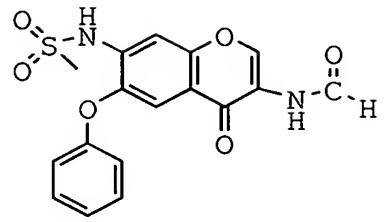
(C40)

4-(2-phenyl-3-pyridinyl)benzenesulfonamide;



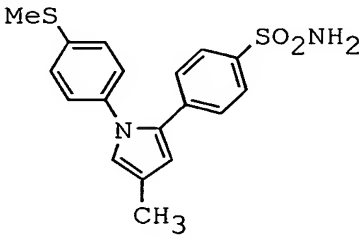
(C41)

N-(2,3-dihydro-1,1-dioxido-6-phenoxy-1,2-benzisothiazol-5-yl)methanesulfonamide; and



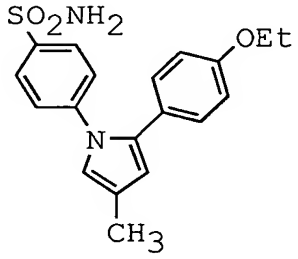
(C42)

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7- yl]methanesulfonamide;



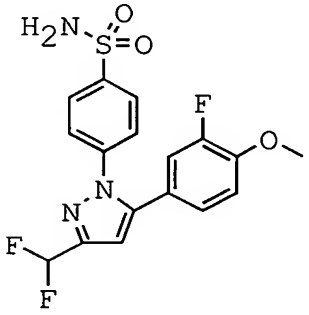
(C43)

4-[4-methyl-1-[4-(methylthio)phenyl]-1H-pyrrol-2-yl]benzenesulfonamide;



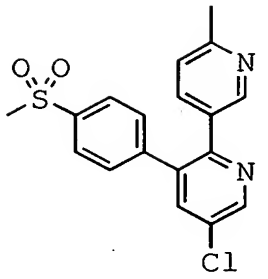
(C44)

4-[2-(4-ethoxyphenyl)-4-methyl-1H-pyrrol-1-yl]benzenesulfonamide;



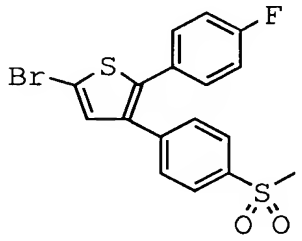
(C45)

deracoxib, 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;



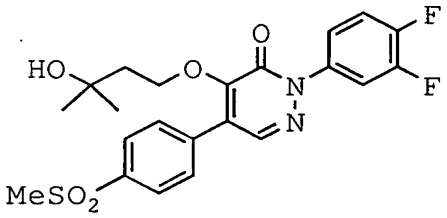
(C46)

MK-663, etoricoxib, 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine;



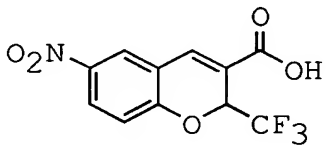
(C47)

DuP 697, 5-bromo-2-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]thiophene;



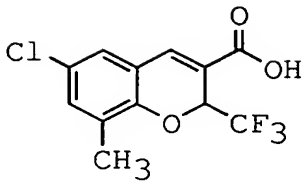
(C48)

ABT-963, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;



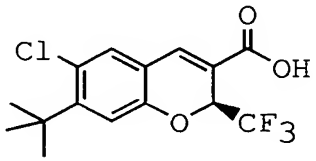
(C49)

6-nitro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;



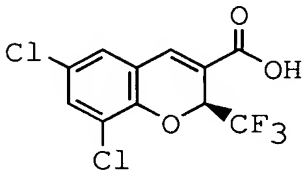
(C50)

6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;



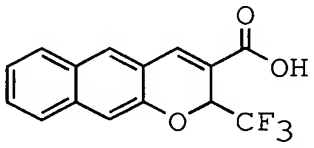
(C51)

(2S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;



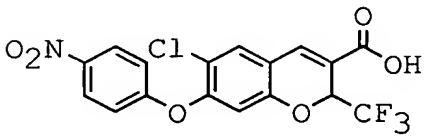
(C52)

(2S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;



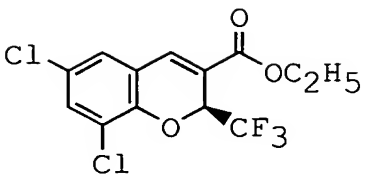
(C53)

2-trifluoromethyl-2H-naphtho[2,3-b]pyran-3-carboxylic acid;



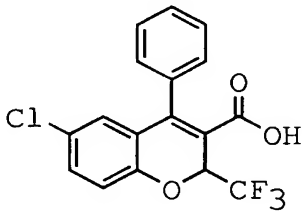
(C54)

6-chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;



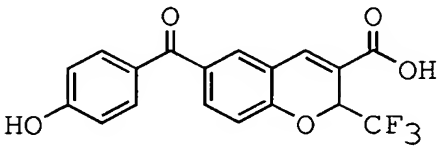
(C55)

(2S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, ethyl ester;



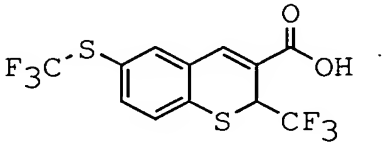
(C56)

6-chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid;



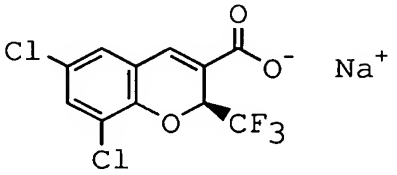
(C57)

6-(4-hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;



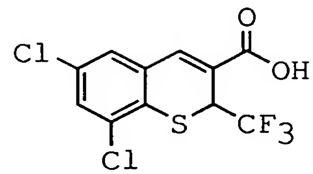
(C58)

2-(trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid;



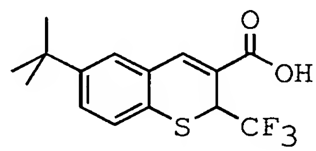
(C59)

(2S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, sodium salt;



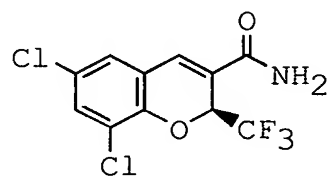
(C60)

6,8-dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;



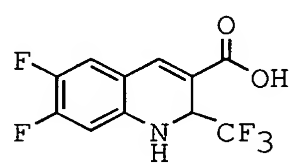
(C61)

6-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid;



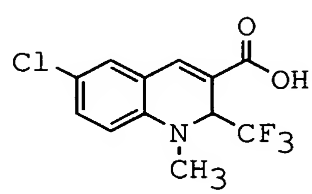
(C62)

(2S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxamide;



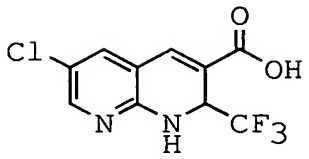
(C63)

6,7-difluoro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid;



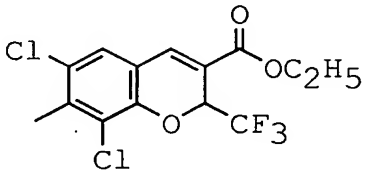
(C64)

6-chloro-1,2-dihydro-1-methyl-2-(trifluoromethyl)-3-quinolinecarboxylic acid;



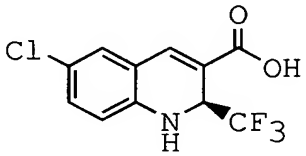
(C65)

6-chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid;



(C66)

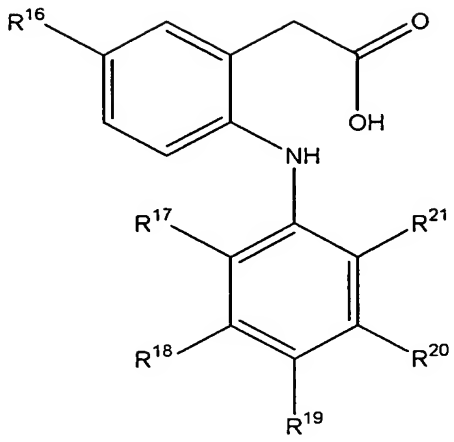
6,8-dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, ethyl ester;



(C67)

(2S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid.

In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula V:



V

wherein R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro; and

R^{21} is chloro, fluoro, trifluoromethyl or methyl, provided that R^{17}, R^{18}, R^{19} and R^{20} are not all fluoro when R^{16} is ethyl and R^{19} is H.

A particularly preferred phenylacetic acid derivative cyclooxygenase-2 selective inhibitor that is described in WO 99/11605 is a compound that has the designation of COX189 (CAS RN 346670-74-4), and that has the structure shown in Formula V,

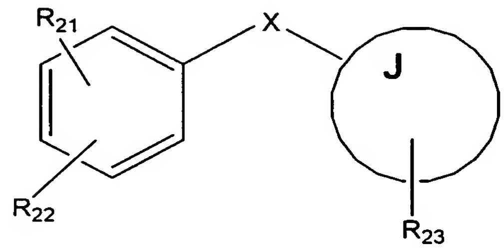
wherein R^{16} is ethyl;

R^{17} and R^{19} are chloro;

R^{18} and R^{20} are hydrogen; and

and R^{21} is methyl.

Other preferred cyclooxygenase-2 selective inhibitors that can be used in the present invention have the general structure shown in formula VI, where the J group is a carbocycle or a heterocycle. Particularly preferred embodiments have the structure:



VI

where:

X is O; J is 1-phenyl; R_{21} is 2-$NHSO_2CH_3$; R_{22} is 4-NO_2; and there is no R_{23} group, (nimesulide), and

X is O; J is 1-oxo-inden-5-yl; R_{21} is 2-F; R_{22} is 4-F; and R_{23} is 6-$NHSO_2CH_3$, (flosulide); and

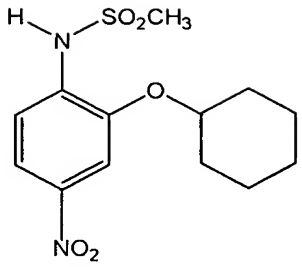
X is O; J is cyclohexyl; R_{21} is 2-$NHSO_2CH_3$; R_{22} is 5-NO_2; and there is no R_{23} group, (NS-398); and

X is S; J is 1-oxo-inden-5-yl; R_{21} is 2-F; R_{22} is 4-F; and R_{23} is 6-$N^{-}SO_2CH_3 \cdot Na^{+}$, (L-745337); and

X is S; J is thiophen-2-yl; R_{21} is 4-F; there is no R_{22} group; and R_{23} is 5-$NHSO_2CH_3$, (RWJ-63556); and

X is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R_{21} is 3-F; R_{22} is 4-F; and R_{23} is 4-(p-SO_2CH_3)C_6H_4, (L-784512).

Further information on the applications of N-(2-cyclohexyloxynitrophenyl)methane sulfonamide (NS-398, CAS RN 123653-11-2), having a structure as shown in formula B-26, have been described by, for example, Yoshimi, N. *et al.*, in *Japanese J. Cancer Res.*, *90(4):*406 - 412 (1999); Falgueyret, J.-P. *et al.*, in *Science Spectra,* available at: http://www.gbhap.com/Science_Spectra/20-1-article.htm

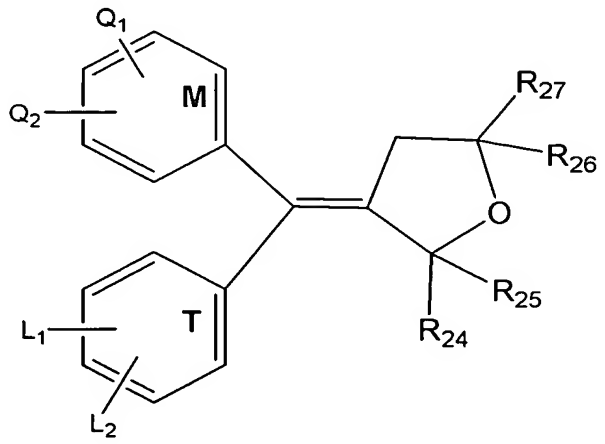


C-68

(06/06/2001); and Iwata, K. *et al.*, in *Jpn. J. Pharmacol., 75(2):*191 - 194 (1997).

An evaluation of the antiinflammatory activity of the cyclooxygenase-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.*, in *J Pharmacol Exp Ther 282*, 1094-1101 (1997).

Other compounds useful as the cyclooxygenase-2 selective inhibitor in the present invention include diarylmethylidenefuran derivatives such as those described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula **VII**:



VII

wherein:

the rings T and M independently are:

a phenyl radical,

a naphthyl radical,

a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or

a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q_1, Q_2, L_1 or L_2 is:

an $--S(O)_n--R$ group, in which n is an integer equal to 0, 1 or 2 and R is a

lower alkyl radical having 1 to 6 carbon atoms or

a lower haloalkyl radical having 1 to 6 carbon atoms, or

an $-SO_2NH_2$ group;

and is located in the para position,

the others independently being:

a hydrogen atom,

a halogen atom,

a lower alkyl radical having 1 to 6 carbon atoms,

a trifluoromethyl radical, or

a lower O-alkyl radical having 1 to 6 carbon atoms,

or

Q_1 and Q_2 or L_1 and L_2 are a methylenedioxy group; and

R_{24}, R_{25}, R_{26} and R_{27} independently are:

a hydrogen atom,

a halogen atom,

a lower alkyl radical having 1 to 6 carbon atoms,

a lower haloalkyl radical having 1 to 6 carbon atoms, or

an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R_{24}, R_{25} or R_{26}, R_{27} are an oxygen atom, or

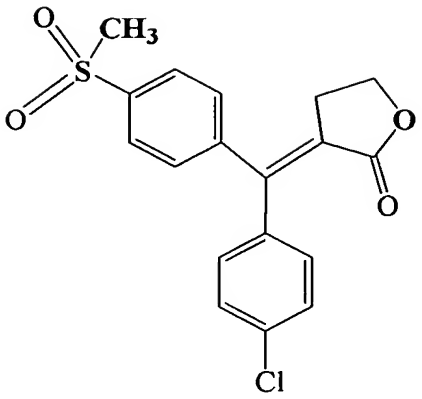
R_{24}, R_{25} or R_{26}, R_{27}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or prodrug thereof.

Particular materials that are included in this family of compounds, and which can serve as the cyclooxygenase-2 selective inhibitor in the present invention, include N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl] benzenesulfonamide.

Preferred cyclooxygenase-2 selective inhibitors that are useful in the present invention include the following individual compounds; darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

In another preferred embodiment of the invention, the compound BMS-347070 having the formula:



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Information about S-33516, mentioned above, can be found in *Current Drugs Headline News*, at http://www.current-drugs.com/NEWS/Inflam1.htm, 10/04/2001, where it was reported that S-33516 is a tetrahydroisoinde derivative which has IC_{50} values of 0.1 and 0.001 mM against cyclooxygenase-1 and cyclooxygenase-2, respectively. In human whole blood, S-33516 was reported to have an ED_{50} = 0.39 mg/kg.

The CAS reference numbers for nonlimiting examples of COX-2 inhibitors are identified in Table 3 below.

Table No. 3. COX-2 Inhibitors

Compound Number	CAS Reference Number
C1	180200-68-4
C2	202409-33-4
C3	212126-32-4
C4	169590-42-5
C5	162011-90-7
C6	181695-72-7
C7	198470-84-7
C8	170569-86-5
C9	187845-71-2
C10	179382-91-3
C11	51803-78-2

Compound Number	CAS Reference Number
C12	189954-13-0
C13	158205-05-1
C14	197239-99-9
C15	197240-09-8
C16	226703-01-1
C17	93014-16-5
C18	197239-97-7
C19	162054-19-5
C20	170569-87-6
C21	279221-13-5
C22	170572-13-1
C23	123653-11-2
C24	80937-31-1
C25	279221-14-6
C26	279221-15-7
C27	187846-16-8
C28	189954-16-3
C29	181485-41-6
C30	187845-80-3
C31	158959-32-1
C32	170570-29-3
C33	177660-77-4
C34	177660-95-6
C35	181695-81-8
C36	197240-14-5
C37	181696-33-3
C38	178816-94-9
C39	178816-61-0
C40	279221-17-9
C41	187845-71-2
C42	123663-49-0
C43	197905-01-4
C44	197904-84-0
C45	169590-41-4

Compound Number	CAS Reference Number
C46	202409-33-4
C47	88149-94-4
C48	266320-83-6
C49	215122-43-3
C50	215122-44-4
C51	215122-74-0
C52	215123-80-1
C53	215122-70-6
C54	264878-87-7
C55	279221-12-4
C56	215123-48-1
C57	215123-03-8
C58	215123-60-7
C59	279221-18-0
C60	215123-61-8
C61	215123-52-7
C62	279221-19-1
C63	215123-64-1
C64	215123-70-9
C65	215123-79-8
C66	215123-91-4
C67	215123-77-6

More preferably, the COX-2 inhibitors that may be used in the present invention include, but are not limited to celecoxib, valdecoxib, parecoxib, rofecoxib, NS-398, deracoxib, Merck MK-663 and ABT-963.

Various classes of cyclooxygenase-2 inhibitors can be prepared as follows. Pyrazoles can be prepared by methods described in WO 95/15316. Pyrazoles can further be prepared by methods described in WO 95/15315. Pyrazoles can also be prepared by methods described in WO 96/03385. Thiophene analogs can be prepared by methods described in WO 95/00501. Preparation of

thiophene analogs is also described in WO 94/15932. Oxazoles can be prepared by the methods described in WO 95/00501. Preparation of oxazoles is also described in WO 94/27980. Isoxazoles can be prepared by the methods described in WO 96/25405. Imidazoles can be prepared by the methods described in WO 96/03388. Preparation of imidazoles is also described in WO 96/03387. Cyclopentene cyclooxygenase-2 inhibitors can be prepared by the methods described in U.S. Patent No. 5,344,991. Preparation of cyclopentene COX-2 inhibitors is also described in WO 95/00501. Terphenyl compounds can be prepared by the methods described in WO 96/16934. Thiazole compounds can be prepared by the methods described in WO 96/03,392. Pyridine compounds can be prepared by the methods described in WO 96/03392. Preparation of pyridine compounds is also described in WO 96/24,585. Benzopyranopyrazolyl compounds can be prepared by the methods described in WO 96/09304. Benzopyran compounds can be prepared by the methods described in WO 98/47890. Preparation of benzopyran compounds is also described in WO 00/23433. Benzopyran compounds can further be prepared by the methods described in U.S. Patent No. 6,077,850. Preparation of benzopyran compounds is further described in U.S. Patent No. 6,034,256. Arylpyridazinones can be prepared by the methods described in WO 00/24719.

The celecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,466,823.

The valdecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,633,272.

The parecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,932,598.

The rofecoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,474,995.

The deracoxib used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,521,207.

The compound MK-663 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 98/03484.

The compound NS-398 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,885,367.

The compound ABT-963 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 00/24719.

The estrogen sex steroid is preferably selected from, but is not limited to, the group consisting of ethinyl estradiol, 17β-estradiol and mestranol.

Still more preferably the estrogen sex steroid is ethinyl estradiol.

The progestin sex steroid is preferably selected from, but is not limited to, the group consisting of levonorgestrel, norethindrone acetate, norgestimate, ethynodiol acetate, desogestrel, norgestrel, gestodene, 3-ketodesogestrel, Org 30659, dienogest, trimegestone and norethindrone.

More preferably the progestin sex steroid is selected from the group consisting of levonorgestrel, norethindrone acetate, norgestimate, ethynodiol acetate, desogestrel, norgestrel and norethindrone.

Even more preferably, the progestin sex steroid is selected from the group consisting of levonorgestrel, norethindrone acetate and norgestimate.

The structures and CAS registry numbers of preferred estrogen and progestin sex steroids are listed in Table No. 4 below.

Table No. 4. Sex Steroid Structures

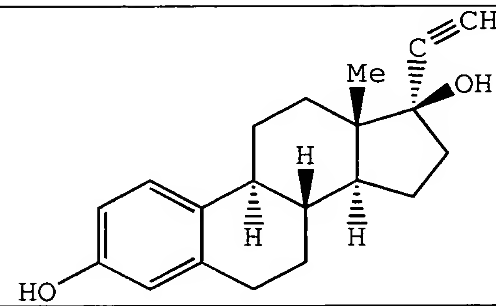
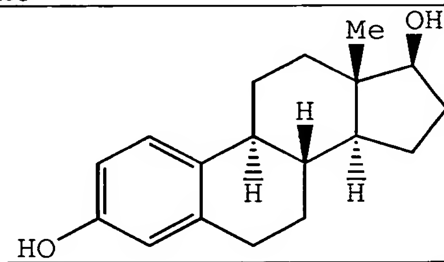
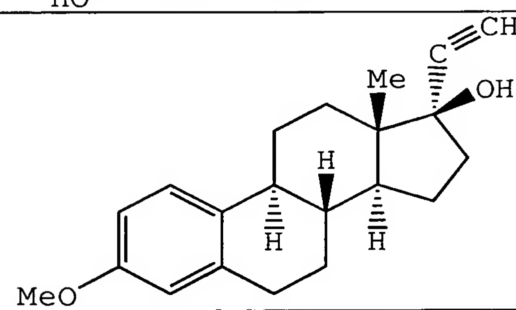
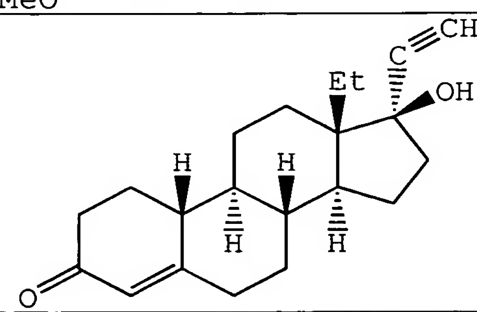
Name	CAS Registry Number	Structure
Ethinyl estradiol	57-63-6	
17β-Estradiol	50-28-2	
Mestranol	72-33-3	
Levonorgestrel	797-63-7	

Table No. 4. Sex Steroid Structures

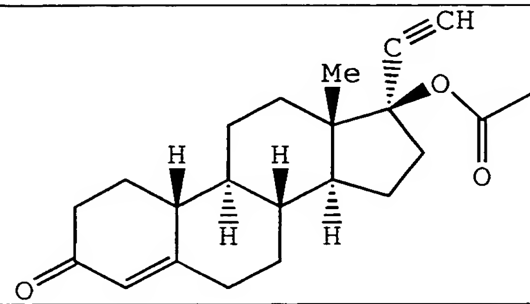
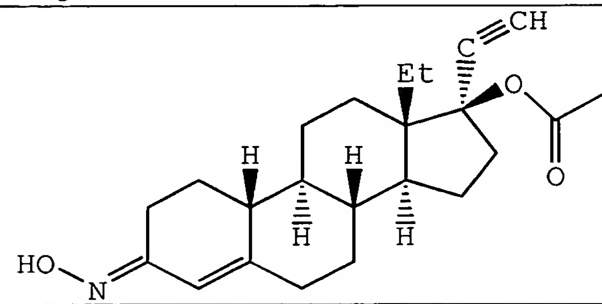
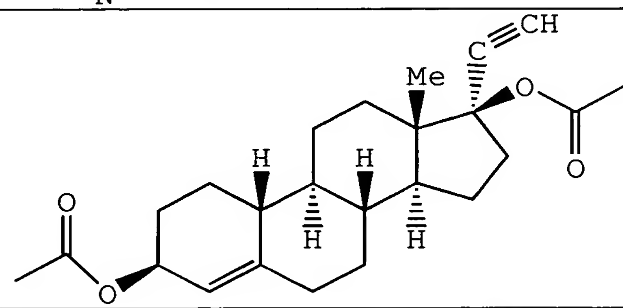
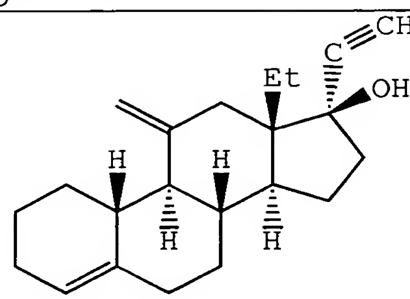
Name	**CAS Registry Number**	**Structure**
Norethindrone acetate	51-98-9	
Norgestimate	35189-28-7	
Ethynodiol diacetate	297-76-7	
Desogestrel	54024-22-5	

Table No. 4. Sex Steroid Structures

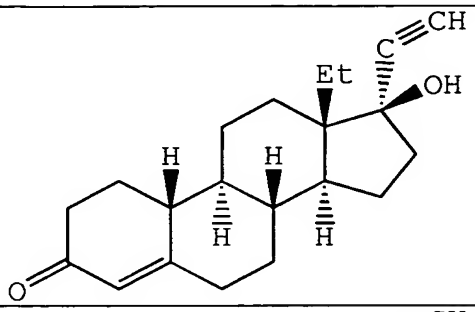
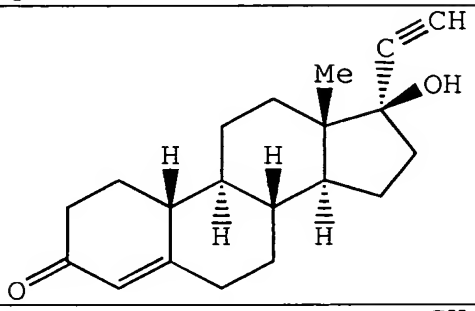
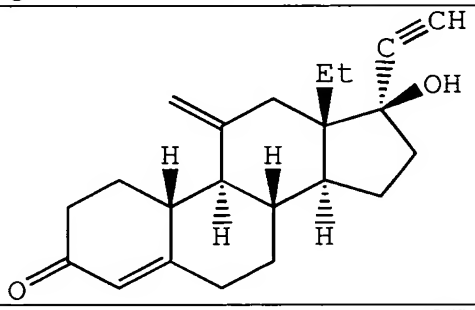
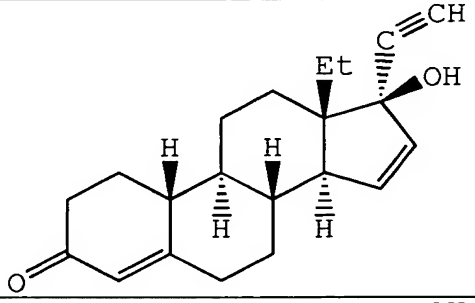
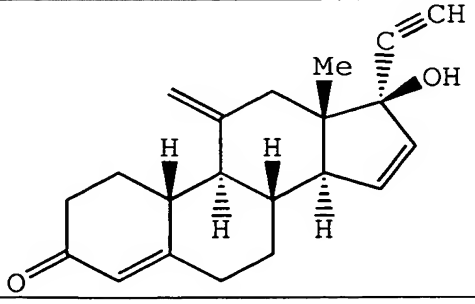
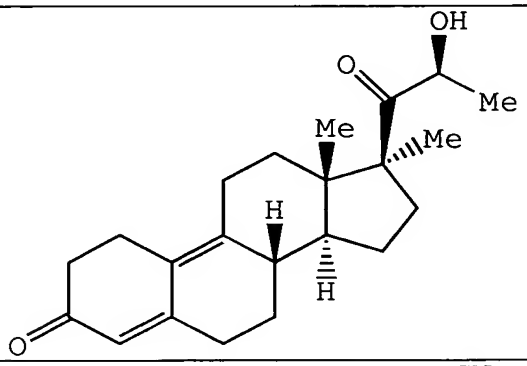
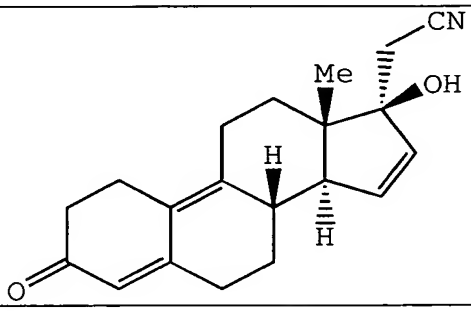
Name	CAS Registry Number	Structure
Norgestrel	6533-00-2	
Norethindrone	68-22-4	
3-Ketodesogestrel	54048-10-1	
Gestodene	60282-87-3	
Org 30659	110072-15-6	

Table No. 4. Sex Steroid Structures

Name	CAS Registry Number	Structure
Trimegestone	74513-62-5	
Dienogest	65928-58-7	

The following references listed in Table No. 5 below, hereby individually incorporated by reference, describe various sex steroids suitable for use in the present invention described herein, and processes for their manufacture.

Table No. 5. Sex Steroid References

Sex Steroid	Reference
Ethinyl estradiol	U.S. Patent No. 3,759,961
17β-Estradiol	U.S. Patent No. 3,274,182
Mestranol	U.S. Patent No. 3,759,961
Levonorgestrel	U.S. Patent No. 3,759,961
Norethindrone acetate	U.S. Patent No. 3,408,371
Norgestimate	U.S. Patent No. 4,027,019
Ethynodiol diacetate	U.S. Patent No. 3,383,384
Desogestrel	U.S. Patent No. 3,927,046

Table No. 5. Sex Steroid References

Sex Steroid	Reference
Norgestrel	U.S. Patent No. 3,892,779
Norethindrone	U.S. Patent No. 3,383,384
3-Ketodesogestrel	U.S. Patent No. 4,371,529
Gestodene	U.S. Patent No. 4,081,537
Org 30659	U.S. Patent No. 5,236,913
Trimegestone	U.S. Patent No. 4,273,771
Dienogest	U.S. Patent No. 4,167,517

The compounds useful in the present invention can have no asymmetric carbon atoms, or, alternatively, the useful compounds can have one or more asymmetric carbon atoms. When the useful compounds have one or more asymmetric carbon atoms, they therefore include racemates and stereoisomers, such as diastereomers and enantiomers, in both pure form and in admixture. Such stereoisomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention.

Isomers may include geometric isomers, for example cis-isomers or trans-isomers across a double bond. All such isomers are contemplated among the compounds useful in the present invention.

The compounds useful in the present invention also include tautomers.

The compounds useful in the present invention also include their salts, solvates and prodrugs.

Dosages, Formulations and Routes of Administration

For the prophylaxis or treatment of the conditions referred to above, the compounds useful in the

combinations and methods of the present invention can be used as the compound *per se*. Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulfonic, and sulfuric acids, and organic acids such as formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, b-hydroxybutyric, galactaric and galacturonic acids.

Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of the above salts can

be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

The compounds useful in the present invention can be presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be present, including other compounds of the present invention. The pharmaceutical compositions of the invention can be prepared by any of the well-known techniques of pharmacy, consisting essentially of admixing the components.

Optionally, the combination of the present invention can comprise a composition comprising a cyclooxygenase-2 inhibiting compound and a sex steroid compound. In such a composition, the cyclooxygenase-2 inhibiting compound and the sex steroid can be present in a single dosage form, for example a pill, a capsule, or a liquid that contains both of the compounds.

These compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic compounds or as a combination of therapeutic compounds.

The amount of compound which is required to achieve the desired biological effect will, of course, depend on a number of factors such as the specific compound chosen, the use for which it is intended, the mode of

administration, and the clinical condition of the recipient.

Dosages

Dosage levels of COX-2 inhibitors on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 1.0 mg to about 1,000 mg and even more preferred levels of about 5 mg to about 500 mg. The amount of active ingredient will vary depending upon the host treated and the particular mode of administration.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the severity of the particular disease being treated and form of administration.

Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from in vitro initially can provide useful guidance on the proper doses for patient administration. Studies in animal models also generally may be used for guidance regarding effective dosages for treatment of cancers in accordance with the present invention. In terms of treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route administered, the condition of the particular patient, etc. Generally speaking, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective in vitro. Thus, where a compound is found to demonstrate in vitro

activity at, e.g., 10 µM, one will desire to administer an amount of the drug that is effective to provide about a 10 µM concentration in vivo. Determination of these parameters is well within the skill of the art. These considerations, as well as effective formulations and administration procedures are well known in the art and are described in standard textbooks.

An estrogen sex steroid at a daily dosage equivalent in estrogenic activity to about 5-75 ug ethinyl estradiol is useful in the treatment of the above conditions, with preferred levels of about 10 ug to about 50 ug and even more preferred levels of about 15 ug to about 35 ug. Actual dosage levels for other estrogen sex steroids may vary relative to the levels listed for ethinyl estradiol. A progestin sex steroid at a daily dosage equivalent in progestinic activity to about 10-600 ug levonorgestrel is useful in the treatment of the above conditions, with preferred levels of about 25 ug to about 400 ug and even more preferred levels of about 50 ug to about 200 ug. Actual dosage levels for other progestin sex steroids may vary relative to the levels listed for levonorgestrel.

The compounds of the present invention can be formulated as a pharmaceutical composition. Such a composition can then be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975. Another discussion of drug formulations can be found in Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980.

Solid dosage forms for oral administration can include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, a contemplated inhibitor compound can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile

injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. A contemplated therapeutic compound can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are solid at ordinary temperatures but

liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.

Treatment Regimen

The dosage regimen to prevent, give relief from, or ameliorate a disease condition having dysmenorrhea as an element of the disease or to protect against or treat a further dysmenorrhea related disorder with the compounds and/or compositions of the present invention is selected in accordance with a variety of factors. These include the type, age, weight, diet, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.

In order to create a reproducible time of menses, specific combinations of daily administration of orally active sex steroids will be used to pharmacologically regulate the onset of menses within a small (24-48 hour) window of time. These steroids will include an estrogenic component and a progestagenic component with the effects of the latter predominating. The use of

such a regimen should also result in less growth of the endometrial lining resulting in a reduced blood loss at the time of menses.

The use of daily orally active sex steroids to regulate endometrial growth will upon their discontinuation result in menses within 48-72 hours. The addition of a cyclooxygenase-2 inhibitor, such as celecoxib, starting 24 hours following discontinuation of the sex steroids will synchronize events such that the cyclooxygenase-2 inhibitor will be reproducibly administered at the time of initiation of increased prostaglandin synthesis triggered by the withdrawal of the steroid hormones. The cyclooxgenase-2 inhibitor can be administered until the end of menses with a variety of regimens. For example, the cyclooxygenase-2 inhibitor can be administered daily (od), twice a day (bid) or three times a day (tid). Thus the invention refers to the sequential administration of daily orally active sex steroids followed by a selective COX-2 inhibitor. This would be administered in a regular schedule (every 28 days) with the sex steroids being administered for 21 days followed by 2-7 days of a cyclooxygenase-2 inhibitor. More preferably, the sex steroids would be administered for 21 days followed by 4-7 days of a cyclooxygenase-2 inhibitor.

Patients undergoing treatment with the compounds or compositions disclosed herein can be routinely monitored to determine the effectiveness of the combination therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimal effective amounts of each type of therapeutic compound are administered at any point in time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over

the course of therapy so that the lowest amount of the therapeutic compounds which together exhibit satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the dysmenorrhea related condition.

A potential advantage of the combination therapy disclosed herein may be reduced dosage amount of any individual therapeutic compound, or all therapeutic compounds, effective in treating dysmenorrhea related conditions. The dosage lowering will provide advantages including reduction of side effects of the individual therapeutic compounds when compared to the monotherapy.

One of the several embodiments of the present invention provides a combination therapy comprising the use of a first amount of a COX-2 inhibitor and a second amount of sex steroids useful in the prophylaxis or treatment of dysmenorrhea, wherein said first and second amounts together comprise an dysmenorrhea-effective amount of said compounds. For example one of the many embodiments of the present invention is a combination therapy regimen comprising therapeutic dosages of a pyrazole COX-2 inhibitor, ethinyl estradiol and levonorgestrel.

The following non-limiting examples serve to illustrate various aspects of the present invention.

Examples

Table 6 illustrates examples of some combinations of the present invention wherein the combination comprises a first amount of a COX-2 inhibitor source, a second amount of a estrogen sex steroid and a third amount of a progestin sex steroid wherein the amounts together comprise an dysmenorrhea-effective amount of the compounds.

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
1	C1	Ethinyl estradiol	Levonorgestrel
2	C2	Ethinyl estradiol	Levonorgestrel
3	C3	Ethinyl estradiol	Levonorgestrel
4	C4	Ethinyl estradiol	Levonorgestrel
5	C5	Ethinyl estradiol	Levonorgestrel
6	C6	Ethinyl estradiol	Levonorgestrel
7	C7	Ethinyl estradiol	Levonorgestrel
8	C8	Ethinyl estradiol	Levonorgestrel
9	C9	Ethinyl estradiol	Levonorgestrel
10	C10	Ethinyl estradiol	Levonorgestrel
11	C11	Ethinyl estradiol	Levonorgestrel
12	C12	Ethinyl estradiol	Levonorgestrel
13	C13	Ethinyl estradiol	Levonorgestrel
14	C14	Ethinyl estradiol	Levonorgestrel
15	C15	Ethinyl estradiol	Levonorgestrel
16	C16	Ethinyl estradiol	Levonorgestrel
17	C17	Ethinyl estradiol	Levonorgestrel
18	C18	Ethinyl estradiol	Levonorgestrel
19	C19	Ethinyl estradiol	Levonorgestrel
20	C20	Ethinyl estradiol	Levonorgestrel
21	C21	Ethinyl estradiol	Levonorgestrel
22	C22	Ethinyl estradiol	Levonorgestrel
23	C23	Ethinyl estradiol	Levonorgestrel
24	C24	Ethinyl estradiol	Levonorgestrel
25	C25	Ethinyl estradiol	Levonorgestrel
26	C26	Ethinyl estradiol	Levonorgestrel
27	C27	Ethinyl estradiol	Levonorgestrel
28	C28	Ethinyl estradiol	Levonorgestrel
29	C29	Ethinyl estradiol	Levonorgestrel
30	C30	Ethinyl estradiol	Levonorgestrel
31	C31	Ethinyl estradiol	Levonorgestrel

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
32	C32	Ethinyl estradiol	Levonorgestrel
33	C33	Ethinyl estradiol	Levonorgestrel
34	C34	Ethinyl estradiol	Levonorgestrel
35	C35	Ethinyl estradiol	Levonorgestrel
36	C36	Ethinyl estradiol	Levonorgestrel
37	C37	Ethinyl estradiol	Levonorgestrel
38	C38	Ethinyl estradiol	Levonorgestrel
39	C39	Ethinyl estradiol	Levonorgestrel
40	C40	Ethinyl estradiol	Levonorgestrel
41	C41	Ethinyl estradiol	Levonorgestrel
42	C42	Ethinyl estradiol	Levonorgestrel
43	C43	Ethinyl estradiol	Levonorgestrel
44	C44	Ethinyl estradiol	Levonorgestrel
45	C45	Ethinyl estradiol	Levonorgestrel
46	C46	Ethinyl estradiol	Levonorgestrel
47	C47	Ethinyl estradiol	Levonorgestrel
48	C48	Ethinyl estradiol	Levonorgestrel
49	C49	Ethinyl estradiol	Levonorgestrel
50	C50	Ethinyl estradiol	Levonorgestrel
51	C51	Ethinyl estradiol	Levonorgestrel
52	C52	Ethinyl estradiol	Levonorgestrel
53	C53	Ethinyl estradiol	Levonorgestrel
54	C54	Ethinyl estradiol	Levonorgestrel
55	C55	Ethinyl estradiol	Levonorgestrel
56	C56	Ethinyl estradiol	Levonorgestrel
57	C57	Ethinyl estradiol	Levonorgestrel
58	C58	Ethinyl estradiol	Levonorgestrel
59	C59	Ethinyl estradiol	Levonorgestrel
60	C60	Ethinyl estradiol	Levonorgestrel
61	C61	Ethinyl estradiol	Levonorgestrel
62	C62	Ethinyl estradiol	Levonorgestrel
63	C63	Ethinyl estradiol	Levonorgestrel

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
64	C64	Ethinyl estradiol	Levonorgestrel
65	C65	Ethinyl estradiol	Levonorgestrel
66	C66	Ethinyl estradiol	Levonorgestrel
67	C67	Ethinyl estradiol	Levonorgestrel
68	C1	Ethinyl estradiol	Norethindrone acetate
69	C2	Ethinyl estradiol	Norethindrone acetate
70	C3	Ethinyl estradiol	Norethindrone acetate
71	C4	Ethinyl estradiol	Norethindrone acetate
72	C5	Ethinyl estradiol	Norethindrone acetate
73	C6	Ethinyl estradiol	Norethindrone acetate
74	C7	Ethinyl estradiol	Norethindrone acetate
75	C8	Ethinyl estradiol	Norethindrone acetate
76	C9	Ethinyl estradiol	Norethindrone acetate
77	C10	Ethinyl estradiol	Norethindrone acetate
78	C11	Ethinyl estradiol	Norethindrone acetate
79	C12	Ethinyl estradiol	Norethindrone acetate
80	C13	Ethinyl estradiol	Norethindrone acetate
81	C14	Ethinyl estradiol	Norethindrone acetate
82	C15	Ethinyl estradiol	Norethindrone acetate
83	C16	Ethinyl estradiol	Norethindrone acetate
84	C17	Ethinyl estradiol	Norethindrone acetate
85	C18	Ethinyl estradiol	Norethindrone acetate
86	C19	Ethinyl estradiol	Norethindrone acetate
87	C20	Ethinyl estradiol	Norethindrone acetate
88	C21	Ethinyl estradiol	Norethindrone acetate
89	C22	Ethinyl estradiol	Norethindrone acetate
90	C23	Ethinyl estradiol	Norethindrone acetate
91	C24	Ethinyl estradiol	Norethindrone acetate
92	C25	Ethinyl estradiol	Norethindrone acetate
93	C26	Ethinyl estradiol	Norethindrone acetate
94	C27	Ethinyl estradiol	Norethindrone acetate
95	C28	Ethinyl estradiol	Norethindrone acetate
96	C29	Ethinyl estradiol	Norethindrone acetate

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
97	C30	Ethinyl estradiol	Norethindrone acetate
98	C31	Ethinyl estradiol	Norethindrone acetate
99	C32	Ethinyl estradiol	Norethindrone acetate
100	C33	Ethinyl estradiol	Norethindrone acetate
101	C34	Ethinyl estradiol	Norethindrone acetate
102	C35	Ethinyl estradiol	Norethindrone acetate
103	C36	Ethinyl estradiol	Norethindrone acetate
104	C37	Ethinyl estradiol	Norethindrone acetate
105	C38	Ethinyl estradiol	Norethindrone acetate
106	C39	Ethinyl estradiol	Norethindrone acetate
107	C40	Ethinyl estradiol	Norethindrone acetate
108	C41	Ethinyl estradiol	Norethindrone acetate
109	C42	Ethinyl estradiol	Norethindrone acetate
110	C43	Ethinyl estradiol	Norethindrone acetate
111	C44	Ethinyl estradiol	Norethindrone acetate
112	C45	Ethinyl estradiol	Norethindrone acetate
113	C46	Ethinyl estradiol	Norethindrone acetate
114	C47	Ethinyl estradiol	Norethindrone acetate
115	C48	Ethinyl estradiol	Norethindrone acetate
116	C49	Ethinyl estradiol	Norethindrone acetate
117	C50	Ethinyl estradiol	Norethindrone acetate
118	C51	Ethinyl estradiol	Norethindrone acetate
119	C52	Ethinyl estradiol	Norethindrone acetate
120	C53	Ethinyl estradiol	Norethindrone acetate
121	C54	Ethinyl estradiol	Norethindrone acetate
122	C55	Ethinyl estradiol	Norethindrone acetate
123	C56	Ethinyl estradiol	Norethindrone acetate
124	C57	Ethinyl estradiol	Norethindrone acetate
125	C58	Ethinyl estradiol	Norethindrone acetate
126	C59	Ethinyl estradiol	Norethindrone acetate
127	C60	Ethinyl estradiol	Norethindrone acetate
128	C61	Ethinyl estradiol	Norethindrone acetate
129	C62	Ethinyl estradiol	Norethindrone acetate

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
130	C63	Ethinyl estradiol	Norethindrone acetate
131	C64	Ethinyl estradiol	Norethindrone acetate
132	C65	Ethinyl estradiol	Norethindrone acetate
133	C66	Ethinyl estradiol	Norethindrone acetate
134	C67	Ethinyl estradiol	Norethindrone acetate
135	C1	Ethinyl estradiol	Norgestimate
136	C2	Ethinyl estradiol	Norgestimate
137	C3	Ethinyl estradiol	Norgestimate
138	C4	Ethinyl estradiol	Norgestimate
139	C5	Ethinyl estradiol	Norgestimate
140	C6	Ethinyl estradiol	Norgestimate
141	C7	Ethinyl estradiol	Norgestimate
142	C8	Ethinyl estradiol	Norgestimate
143	C9	Ethinyl estradiol	Norgestimate
144	C10	Ethinyl estradiol	Norgestimate
145	C11	Ethinyl estradiol	Norgestimate
146	C12	Ethinyl estradiol	Norgestimate
147	C13	Ethinyl estradiol	Norgestimate
148	C14	Ethinyl estradiol	Norgestimate
149	C15	Ethinyl estradiol	Norgestimate
150	C16	Ethinyl estradiol	Norgestimate
151	C17	Ethinyl estradiol	Norgestimate
152	C18	Ethinyl estradiol	Norgestimate
153	C19	Ethinyl estradiol	Norgestimate
154	C20	Ethinyl estradiol	Norgestimate
155	C21	Ethinyl estradiol	Norgestimate
156	C22	Ethinyl estradiol	Norgestimate
157	C23	Ethinyl estradiol	Norgestimate
158	C24	Ethinyl estradiol	Norgestimate
159	C25	Ethinyl estradiol	Norgestimate
160	C26	Ethinyl estradiol	Norgestimate
161	C27	Ethinyl estradiol	Norgestimate
162	C28	Ethinyl estradiol	Norgestimate

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
163	C29	Ethinyl estradiol	Norgestimate
164	C30	Ethinyl estradiol	Norgestimate
165	C31	Ethinyl estradiol	Norgestimate
166	C32	Ethinyl estradiol	Norgestimate
167	C33	Ethinyl estradiol	Norgestimate
168	C34	Ethinyl estradiol	Norgestimate
169	C35	Ethinyl estradiol	Norgestimate
170	C36	Ethinyl estradiol	Norgestimate
171	C37	Ethinyl estradiol	Norgestimate
172	C38	Ethinyl estradiol	Norgestimate
173	C39	Ethinyl estradiol	Norgestimate
174	C40	Ethinyl estradiol	Norgestimate
175	C41	Ethinyl estradiol	Norgestimate
176	C42	Ethinyl estradiol	Norgestimate
177	C43	Ethinyl estradiol	Norgestimate
178	C44	Ethinyl estradiol	Norgestimate
179	C45	Ethinyl estradiol	Norgestimate
180	C46	Ethinyl estradiol	Norgestimate
181	C47	Ethinyl estradiol	Norgestimate
182	C48	Ethinyl estradiol	Norgestimate
183	C49	Ethinyl estradiol	Norgestimate
184	C50	Ethinyl estradiol	Norgestimate
185	C51	Ethinyl estradiol	Norgestimate
186	C52	Ethinyl estradiol	Norgestimate
187	C53	Ethinyl estradiol	Norgestimate
188	C54	Ethinyl estradiol	Norgestimate
189	C55	Ethinyl estradiol	Norgestimate
190	C56	Ethinyl estradiol	Norgestimate
191	C57	Ethinyl estradiol	Norgestimate
192	C58	Ethinyl estradiol	Norgestimate
193	C59	Ethinyl estradiol	Norgestimate
194	C60	Ethinyl estradiol	Norgestimate
195	C61	Ethinyl estradiol	Norgestimate

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
196	C62	Ethinyl estradiol	Norgestimate
197	C63	Ethinyl estradiol	Norgestimate
198	C64	Ethinyl estradiol	Norgestimate
199	C65	Ethinyl estradiol	Norgestimate
200	C66	Ethinyl estradiol	Norgestimate
201	C67	Ethinyl estradiol	Norgestimate
202	C1	Ethinyl estradiol	Ethynodiol diacetate
203	C2	Ethinyl estradiol	Ethynodiol diacetate

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
204	C3	Ethinyl estradiol	Ethynodiol diacetate
205	C4	Ethinyl estradiol	Ethynodiol diacetate
206	C5	Ethinyl estradiol	Ethynodiol diacetate
207	C6	Ethinyl estradiol	Ethynodiol diacetate
208	C7	Ethinyl estradiol	Ethynodiol diacetate
209	C8	Ethinyl estradiol	Ethynodiol diacetate
210	C9	Ethinyl estradiol	Ethynodiol diacetate
211	C10	Ethinyl estradiol	Ethynodiol diacetate
212	C11	Ethinyl estradiol	Ethynodiol diacetate
213	C12	Ethinyl estradiol	Ethynodiol diacetate
214	C13	Ethinyl estradiol	Ethynodiol diacetate
215	C14	Ethinyl estradiol	Ethynodiol diacetate
216	C15	Ethinyl estradiol	Ethynodiol diacetate
217	C16	Ethinyl estradiol	Ethynodiol diacetate
218	C17	Ethinyl estradiol	Ethynodiol diacetate
219	C18	Ethinyl estradiol	Ethynodiol diacetate
220	C19	Ethinyl estradiol	Ethynodiol diacetate
221	C20	Ethinyl estradiol	Ethynodiol diacetate
222	C21	Ethinyl estradiol	Ethynodiol diacetate
223	C22	Ethinyl estradiol	Ethynodiol diacetate
224	C23	Ethinyl estradiol	Ethynodiol diacetate
225	C24	Ethinyl estradiol	Ethynodiol diacetate
226	C25	Ethinyl estradiol	Ethynodiol diacetate
227	C26	Ethinyl estradiol	Ethynodiol diacetate
228	C27	Ethinyl estradiol	Ethynodiol diacetate
229	C28	Ethinyl estradiol	Ethynodiol diacetate
230	C29	Ethinyl estradiol	Ethynodiol diacetate
231	C30	Ethinyl estradiol	Ethynodiol diacetate
232	C31	Ethinyl estradiol	Ethynodiol diacetate
233	C32	Ethinyl estradiol	Ethynodiol diacetate
234	C33	Ethinyl estradiol	Ethynodiol diacetate
235	C34	Ethinyl estradiol	Ethynodiol diacetate

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
236	C35	Ethinyl estradiol	Ethynodiol diacetate
237	C36	Ethinyl estradiol	Ethynodiol diacetate
238	C37	Ethinyl estradiol	Ethynodiol diacetate
239	C38	Ethinyl estradiol	Ethynodiol diacetate
240	C39	Ethinyl estradiol	Ethynodiol diacetate
241	C40	Ethinyl estradiol	Ethynodiol diacetate
242	C41	Ethinyl estradiol	Ethynodiol diacetate
243	C42	Ethinyl estradiol	Ethynodiol diacetate
244	C43	Ethinyl estradiol	Ethynodiol diacetate
245	C44	Ethinyl estradiol	Ethynodiol diacetate
246	C45	Ethinyl estradiol	Ethynodiol diacetate
247	C46	Ethinyl estradiol	Ethynodiol diacetate
248	C47	Ethinyl estradiol	Ethynodiol diacetate
249	C48	Ethinyl estradiol	Ethynodiol diacetate
250	C49	Ethinyl estradiol	Ethynodiol diacetate
251	C50	Ethinyl estradiol	Ethynodiol diacetate
252	C51	Ethinyl estradiol	Ethynodiol diacetate
253	C52	Ethinyl estradiol	Ethynodiol diacetate
254	C53	Ethinyl estradiol	Ethynodiol diacetate
255	C54	Ethinyl estradiol	Ethynodiol diacetate
256	C55	Ethinyl estradiol	Ethynodiol diacetate
257	C56	Ethinyl estradiol	Ethynodiol diacetate
258	C57	Ethinyl estradiol	Ethynodiol diacetate
259	C58	Ethinyl estradiol	Ethynodiol diacetate
260	C59	Ethinyl estradiol	Ethynodiol diacetate
261	C60	Ethinyl estradiol	Ethynodiol diacetate
262	C61	Ethinyl estradiol	Ethynodiol diacetate
263	C62	Ethinyl estradiol	Ethynodiol diacetate
264	C63	Ethinyl estradiol	Ethynodiol diacetate
265	C64	Ethinyl estradiol	Ethynodiol diacetate
266	C65	Ethinyl estradiol	Ethynodiol diacetate
267	C66	Ethinyl estradiol	Ethynodiol diacetate

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
268	C67	Ethinyl estradiol	Ethynodiol diacetate
269	C1	Ethinyl estradiol	Desogestrel
270	C2	Ethinyl estradiol	Desogestrel
271	C3	Ethinyl estradiol	Desogestrel
272	C4	Ethinyl estradiol	Desogestrel
273	C5	Ethinyl estradiol	Desogestrel
274	C6	Ethinyl estradiol	Desogestrel
275	C7	Ethinyl estradiol	Desogestrel
276	C8	Ethinyl estradiol	Desogestrel
277	C9	Ethinyl estradiol	Desogestrel
278	C10	Ethinyl estradiol	Desogestrel
279	C11	Ethinyl estradiol	Desogestrel
280	C12	Ethinyl estradiol	Desogestrel
281	C13	Ethinyl estradiol	Desogestrel
282	C14	Ethinyl estradiol	Desogestrel
283	C15	Ethinyl estradiol	Desogestrel
284	C16	Ethinyl estradiol	Desogestrel
285	C17	Ethinyl estradiol	Desogestrel
286	C18	Ethinyl estradiol	Desogestrel
287	C19	Ethinyl estradiol	Desogestrel
288	C20	Ethinyl estradiol	Desogestrel
289	C21	Ethinyl estradiol	Desogestrel
290	C22	Ethinyl estradiol	Desogestrel
291	C23	Ethinyl estradiol	Desogestrel
292	C24	Ethinyl estradiol	Desogestrel
293	C25	Ethinyl estradiol	Desogestrel
294	C26	Ethinyl estradiol	Desogestrel
295	C27	Ethinyl estradiol	Desogestrel
296	C28	Ethinyl estradiol	Desogestrel
297	C29	Ethinyl estradiol	Desogestrel
298	C30	Ethinyl estradiol	Desogestrel
299	C31	Ethinyl estradiol	Desogestrel

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
300	C32	Ethinyl estradiol	Desogestrel
301	C33	Ethinyl estradiol	Desogestrel
302	C34	Ethinyl estradiol	Desogestrel
303	C35	Ethinyl estradiol	Desogestrel
304	C36	Ethinyl estradiol	Desogestrel
305	C37	Ethinyl estradiol	Desogestrel
306	C38	Ethinyl estradiol	Desogestrel
307	C39	Ethinyl estradiol	Desogestrel
308	C40	Ethinyl estradiol	Desogestrel
309	C41	Ethinyl estradiol	Desogestrel
310	C42	Ethinyl estradiol	Desogestrel
311	C43	Ethinyl estradiol	Desogestrel
312	C44	Ethinyl estradiol	Desogestrel
313	C45	Ethinyl estradiol	Desogestrel
314	C46	Ethinyl estradiol	Desogestrel
315	C47	Ethinyl estradiol	Desogestrel
316	C48	Ethinyl estradiol	Desogestrel
317	C49	Ethinyl estradiol	Desogestrel
318	C50	Ethinyl estradiol	Desogestrel
319	C51	Ethinyl estradiol	Desogestrel
320	C52	Ethinyl estradiol	Desogestrel
321	C53	Ethinyl estradiol	Desogestrel
322	C54	Ethinyl estradiol	Desogestrel
323	C55	Ethinyl estradiol	Desogestrel
324	C56	Ethinyl estradiol	Desogestrel
325	C57	Ethinyl estradiol	Desogestrel
326	C58	Ethinyl estradiol	Desogestrel
327	C59	Ethinyl estradiol	Desogestrel
328	C60	Ethinyl estradiol	Desogestrel
329	C61	Ethinyl estradiol	Desogestrel
330	C62	Ethinyl estradiol	Desogestrel
331	C63	Ethinyl estradiol	Desogestrel

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
332	C64	Ethinyl estradiol	Desogestrel
333	C65	Ethinyl estradiol	Desogestrel
334	C66	Ethinyl estradiol	Desogestrel
335	C67	Ethinyl estradiol	Desogestrel
336	C1	Ethinyl estradiol	Norgestrel
337	C2	Ethinyl estradiol	Norgestrel
338	C3	Ethinyl estradiol	Norgestrel
339	C4	Ethinyl estradiol	Norgestrel
340	C5	Ethinyl estradiol	Norgestrel
341	C6	Ethinyl estradiol	Norgestrel
342	C7	Ethinyl estradiol	Norgestrel
343	C8	Ethinyl estradiol	Norgestrel
344	C9	Ethinyl estradiol	Norgestrel
345	C10	Ethinyl estradiol	Norgestrel
346	C11	Ethinyl estradiol	Norgestrel
347	C12	Ethinyl estradiol	Norgestrel
348	C13	Ethinyl estradiol	Norgestrel
349	C14	Ethinyl estradiol	Norgestrel
350	C15	Ethinyl estradiol	Norgestrel
351	C16	Ethinyl estradiol	Norgestrel
352	C17	Ethinyl estradiol	Norgestrel
353	C18	Ethinyl estradiol	Norgestrel
354	C19	Ethinyl estradiol	Norgestrel
355	C20	Ethinyl estradiol	Norgestrel
356	C21	Ethinyl estradiol	Norgestrel
357	C22	Ethinyl estradiol	Norgestrel
358	C23	Ethinyl estradiol	Norgestrel
359	C24	Ethinyl estradiol	Norgestrel
360	C25	Ethinyl estradiol	Norgestrel
361	C26	Ethinyl estradiol	Norgestrel
362	C27	Ethinyl estradiol	Norgestrel
363	C28	Ethinyl estradiol	Norgestrel

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
364	C29	Ethinyl estradiol	Norgestrel
365	C30	Ethinyl estradiol	Norgestrel
366	C31	Ethinyl estradiol	Norgestrel
367	C32	Ethinyl estradiol	Norgestrel
368	C33	Ethinyl estradiol	Norgestrel
369	C34	Ethinyl estradiol	Norgestrel
370	C35	Ethinyl estradiol	Norgestrel
371	C36	Ethinyl estradiol	Norgestrel
372	C37	Ethinyl estradiol	Norgestrel
373	C38	Ethinyl estradiol	Norgestrel
374	C39	Ethinyl estradiol	Norgestrel
375	C40	Ethinyl estradiol	Norgestrel
376	C41	Ethinyl estradiol	Norgestrel
377	C42	Ethinyl estradiol	Norgestrel
378	C43	Ethinyl estradiol	Norgestrel
379	C44	Ethinyl estradiol	Norgestrel
380	C45	Ethinyl estradiol	Norgestrel
381	C46	Ethinyl estradiol	Norgestrel
382	C47	Ethinyl estradiol	Norgestrel
383	C48	Ethinyl estradiol	Norgestrel
384	C49	Ethinyl estradiol	Norgestrel
385	C50	Ethinyl estradiol	Norgestrel
386	C51	Ethinyl estradiol	Norgestrel
387	C52	Ethinyl estradiol	Norgestrel
388	C53	Ethinyl estradiol	Norgestrel
389	C54	Ethinyl estradiol	Norgestrel
390	C55	Ethinyl estradiol	Norgestrel
391	C56	Ethinyl estradiol	Norgestrel
392	C57	Ethinyl estradiol	Norgestrel
393	C58	Ethinyl estradiol	Norgestrel
394	C59	Ethinyl estradiol	Norgestrel
395	C60	Ethinyl estradiol	Norgestrel

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
396	C61	Ethinyl estradiol	Norgestrel
397	C62	Ethinyl estradiol	Norgestrel
398	C63	Ethinyl estradiol	Norgestrel
399	C64	Ethinyl estradiol	Norgestrel
400	C65	Ethinyl estradiol	Norgestrel
401	C66	Ethinyl estradiol	Norgestrel
402	C67	Ethinyl estradiol	Norgestrel
403	C1	Ethinyl estradiol	Norethindrone
404	C2	Ethinyl estradiol	Norethindrone
405	C3	Ethinyl estradiol	Norethindrone
406	C4	Ethinyl estradiol	Norethindrone
407	C5	Ethinyl estradiol	Norethindrone
408	C6	Ethinyl estradiol	Norethindrone
409	C7	Ethinyl estradiol	Norethindrone
410	C8	Ethinyl estradiol	Norethindrone
411	C9	Ethinyl estradiol	Norethindrone
412	C10	Ethinyl estradiol	Norethindrone
413	C11	Ethinyl estradiol	Norethindrone
414	C12	Ethinyl estradiol	Norethindrone
415	C13	Ethinyl estradiol	Norethindrone
416	C14	Ethinyl estradiol	Norethindrone
417	C15	Ethinyl estradiol	Norethindrone
418	C16	Ethinyl estradiol	Norethindrone
419	C17	Ethinyl estradiol	Norethindrone
420	C18	Ethinyl estradiol	Norethindrone
421	C19	Ethinyl estradiol	Norethindrone
422	C20	Ethinyl estradiol	Norethindrone
423	C21	Ethinyl estradiol	Norethindrone
424	C22	Ethinyl estradiol	Norethindrone
425	C23	Ethinyl estradiol	Norethindrone
426	C24	Ethinyl estradiol	Norethindrone
427	C25	Ethinyl estradiol	Norethindrone

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
428	C26	Ethinyl estradiol	Norethindrone
429	C27	Ethinyl estradiol	Norethindrone
430	C28	Ethinyl estradiol	Norethindrone
431	C29	Ethinyl estradiol	Norethindrone
432	C30	Ethinyl estradiol	Norethindrone
433	C31	Ethinyl estradiol	Norethindrone
434	C32	Ethinyl estradiol	Norethindrone
435	C33	Ethinyl estradiol	Norethindrone
436	C34	Ethinyl estradiol	Norethindrone
437	C35	Ethinyl estradiol	Norethindrone
438	C36	Ethinyl estradiol	Norethindrone
439	C37	Ethinyl estradiol	Norethindrone
440	C38	Ethinyl estradiol	Norethindrone
441	C39	Ethinyl estradiol	Norethindrone
442	C40	Ethinyl estradiol	Norethindrone
443	C41	Ethinyl estradiol	Norethindrone
444	C42	Ethinyl estradiol	Norethindrone
445	C43	Ethinyl estradiol	Norethindrone
446	C44	Ethinyl estradiol	Norethindrone
447	C45	Ethinyl estradiol	Norethindrone
448	C46	Ethinyl estradiol	Norethindrone
449	C47	Ethinyl estradiol	Norethindrone
450	C48	Ethinyl estradiol	Norethindrone
451	C49	Ethinyl estradiol	Norethindrone
452	C50	Ethinyl estradiol	Norethindrone
453	C51	Ethinyl estradiol	Norethindrone
454	C52	Ethinyl estradiol	Norethindrone
455	C53	Ethinyl estradiol	Norethindrone
456	C54	Ethinyl estradiol	Norethindrone
457	C55	Ethinyl estradiol	Norethindrone
458	C56	Ethinyl estradiol	Norethindrone
459	C57	Ethinyl estradiol	Norethindrone

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
460	C58	Ethinyl estradiol	Norethindrone
461	C59	Ethinyl estradiol	Norethindrone
462	C60	Ethinyl estradiol	Norethindrone
463	C61	Ethinyl estradiol	Norethindrone
464	C62	Ethinyl estradiol	Norethindrone
465	C63	Ethinyl estradiol	Norethindrone
466	C64	Ethinyl estradiol	Norethindrone
467	C65	Ethinyl estradiol	Norethindrone
468	C66	Ethinyl estradiol	Norethindrone
469	C67	Ethinyl estradiol	Norethindrone
470	C1	Ethinyl estradiol	3-Ketodesogestrel
471	C2	Ethinyl estradiol	3-Ketodesogestrel
472	C3	Ethinyl estradiol	3-Ketodesogestrel
473	C4	Ethinyl estradiol	3-Ketodesogestrel
474	C5	Ethinyl estradiol	3-Ketodesogestrel
475	C6	Ethinyl estradiol	3-Ketodesogestrel
476	C7	Ethinyl estradiol	3-Ketodesogestrel
477	C8	Ethinyl estradiol	3-Ketodesogestrel
478	C9	Ethinyl estradiol	3-Ketodesogestrel
479	C10	Ethinyl estradiol	3-Ketodesogestrel
480	C11	Ethinyl estradiol	3-Ketodesogestrel
481	C12	Ethinyl estradiol	3-Ketodesogestrel
482	C13	Ethinyl estradiol	3-Ketodesogestrel
483	C14	Ethinyl estradiol	3-Ketodesogestrel
484	C15	Ethinyl estradiol	3-Ketodesogestrel
485	C16	Ethinyl estradiol	3-Ketodesogestrel
486	C17	Ethinyl estradiol	3-Ketodesogestrel
487	C18	Ethinyl estradiol	3-Ketodesogestrel
488	C19	Ethinyl estradiol	3-Ketodesogestrel
489	C20	Ethinyl estradiol	3-Ketodesogestrel
490	C21	Ethinyl estradiol	3-Ketodesogestrel
491	C22	Ethinyl estradiol	3-Ketodesogestrel

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
492	C23	Ethinyl estradiol	3-Ketodesogestrel
493	C24	Ethinyl estradiol	3-Ketodesogestrel
494	C25	Ethinyl estradiol	3-Ketodesogestrel
495	C26	Ethinyl estradiol	3-Ketodesogestrel
496	C27	Ethinyl estradiol	3-Ketodesogestrel
497	C28	Ethinyl estradiol	3-Ketodesogestrel
498	C29	Ethinyl estradiol	3-Ketodesogestrel
499	C30	Ethinyl estradiol	3-Ketodesogestrel
500	C31	Ethinyl estradiol	3-Ketodesogestrel
501	C32	Ethinyl estradiol	3-Ketodesogestrel
502	C33	Ethinyl estradiol	3-Ketodesogestrel
503	C34	Ethinyl estradiol	3-Ketodesogestrel
504	C35	Ethinyl estradiol	3-Ketodesogestrel
505	C36	Ethinyl estradiol	3-Ketodesogestrel
506	C37	Ethinyl estradiol	3-Ketodesogestrel
507	C38	Ethinyl estradiol	3-Ketodesogestrel
508	C39	Ethinyl estradiol	3-Ketodesogestrel
509	C40	Ethinyl estradiol	3-Ketodesogestrel
510	C41	Ethinyl estradiol	3-Ketodesogestrel
511	C42	Ethinyl estradiol	3-Ketodesogestrel
512	C43	Ethinyl estradiol	3-Ketodesogestrel
513	C44	Ethinyl estradiol	3-Ketodesogestrel
514	C45	Ethinyl estradiol	3-Ketodesogestrel
515	C46	Ethinyl estradiol	3-Ketodesogestrel
516	C47	Ethinyl estradiol	3-Ketodesogestrel
517	C48	Ethinyl estradiol	3-Ketodesogestrel
518	C49	Ethinyl estradiol	3-Ketodesogestrel
519	C50	Ethinyl estradiol	3-Ketodesogestrel
520	C51	Ethinyl estradiol	3-Ketodesogestrel
521	C52	Ethinyl estradiol	3-Ketodesogestrel
522	C53	Ethinyl estradiol	3-Ketodesogestrel
523	C54	Ethinyl estradiol	3-Ketodesogestrel

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
524	C55	Ethinyl estradiol	3-Ketodesogestrel
525	C56	Ethinyl estradiol	3-Ketodesogestrel
526	C57	Ethinyl estradiol	3-Ketodesogestrel
527	C58	Ethinyl estradiol	3-Ketodesogestrel
528	C59	Ethinyl estradiol	3-Ketodesogestrel
529	C60	Ethinyl estradiol	3-Ketodesogestrel
530	C61	Ethinyl estradiol	3-Ketodesogestrel
531	C62	Ethinyl estradiol	3-Ketodesogestrel
532	C63	Ethinyl estradiol	3-Ketodesogestrel
533	C64	Ethinyl estradiol	3-Ketodesogestrel
534	C65	Ethinyl estradiol	3-Ketodesogestrel
535	C66	Ethinyl estradiol	3-Ketodesogestrel
536	C67	Ethinyl estradiol	3-Ketodesogestrel
537	C1	Ethinyl estradiol	Gestodene
538	C2	Ethinyl estradiol	Gestodene
539	C3	Ethinyl estradiol	Gestodene
540	C4	Ethinyl estradiol	Gestodene
541	C5	Ethinyl estradiol	Gestodene
542	C6	Ethinyl estradiol	Gestodene
543	C7	Ethinyl estradiol	Gestodene
544	C8	Ethinyl estradiol	Gestodene
545	C9	Ethinyl estradiol	Gestodene
546	C10	Ethinyl estradiol	Gestodene
547	C11	Ethinyl estradiol	Gestodene
548	C12	Ethinyl estradiol	Gestodene
549	C13	Ethinyl estradiol	Gestodene
550	C14	Ethinyl estradiol	Gestodene
551	C15	Ethinyl estradiol	Gestodene
552	C16	Ethinyl estradiol	Gestodene
553	C17	Ethinyl estradiol	Gestodene
554	C18	Ethinyl estradiol	Gestodene
555	C19	Ethinyl estradiol	Gestodene

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
556	C20	Ethinyl estradiol	Gestodene
557	C21	Ethinyl estradiol	Gestodene
558	C22	Ethinyl estradiol	Gestodene
559	C23	Ethinyl estradiol	Gestodene
560	C24	Ethinyl estradiol	Gestodene
561	C25	Ethinyl estradiol	Gestodene
562	C26	Ethinyl estradiol	Gestodene
563	C27	Ethinyl estradiol	Gestodene
564	C28	Ethinyl estradiol	Gestodene
565	C29	Ethinyl estradiol	Gestodene
566	C30	Ethinyl estradiol	Gestodene
567	C31	Ethinyl estradiol	Gestodene
568	C32	Ethinyl estradiol	Gestodene
569	C33	Ethinyl estradiol	Gestodene
570	C34	Ethinyl estradiol	Gestodene
571	C35	Ethinyl estradiol	Gestodene
572	C36	Ethinyl estradiol	Gestodene
573	C37	Ethinyl estradiol	Gestodene
574	C38	Ethinyl estradiol	Gestodene
575	C39	Ethinyl estradiol	Gestodene
576	C40	Ethinyl estradiol	Gestodene
577	C41	Ethinyl estradiol	Gestodene
578	C42	Ethinyl estradiol	Gestodene
579	C43	Ethinyl estradiol	Gestodene
580	C44	Ethinyl estradiol	Gestodene
581	C45	Ethinyl estradiol	Gestodene
582	C46	Ethinyl estradiol	Gestodene
583	C47	Ethinyl estradiol	Gestodene
584	C48	Ethinyl estradiol	Gestodene
585	C49	Ethinyl estradiol	Gestodene
586	C50	Ethinyl estradiol	Gestodene
587	C51	Ethinyl estradiol	Gestodene

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
588	C52	Ethinyl estradiol	Gestodene
589	C53	Ethinyl estradiol	Gestodene
590	C54	Ethinyl estradiol	Gestodene
591	C55	Ethinyl estradiol	Gestodene
592	C56	Ethinyl estradiol	Gestodene
593	C57	Ethinyl estradiol	Gestodene
594	C58	Ethinyl estradiol	Gestodene
595	C59	Ethinyl estradiol	Gestodene
596	C60	Ethinyl estradiol	Gestodene
597	C61	Ethinyl estradiol	Gestodene
598	C62	Ethinyl estradiol	Gestodene
599	C63	Ethinyl estradiol	Gestodene
600	C64	Ethinyl estradiol	Gestodene
601	C65	Ethinyl estradiol	Gestodene
602	C66	Ethinyl estradiol	Gestodene
603	C67	Ethinyl estradiol	Gestodene
604	C1	Ethinyl estradiol	Org 30659
605	C2	Ethinyl estradiol	Org 30659
606	C3	Ethinyl estradiol	Org 30659
607	C4	Ethinyl estradiol	Org 30659
608	C5	Ethinyl estradiol	Org 30659
609	C6	Ethinyl estradiol	Org 30659
610	C7	Ethinyl estradiol	Org 30659
611	C8	Ethinyl estradiol	Org 30659
612	C9	Ethinyl estradiol	Org 30659
613	C10	Ethinyl estradiol	Org 30659
614	C11	Ethinyl estradiol	Org 30659
615	C12	Ethinyl estradiol	Org 30659
616	C13	Ethinyl estradiol	Org 30659
617	C14	Ethinyl estradiol	Org 30659
618	C15	Ethinyl estradiol	Org 30659
619	C16	Ethinyl estradiol	Org 30659

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
620	C17	Ethinyl estradiol	Org 30659
621	C18	Ethinyl estradiol	Org 30659
622	C19	Ethinyl estradiol	Org 30659
623	C20	Ethinyl estradiol	Org 30659
624	C21	Ethinyl estradiol	Org 30659
625	C22	Ethinyl estradiol	Org 30659
626	C23	Ethinyl estradiol	Org 30659
627	C24	Ethinyl estradiol	Org 30659
628	C25	Ethinyl estradiol	Org 30659
629	C26	Ethinyl estradiol	Org 30659
630	C27	Ethinyl estradiol	Org 30659
631	C28	Ethinyl estradiol	Org 30659
632	C29	Ethinyl estradiol	Org 30659
633	C30	Ethinyl estradiol	Org 30659
634	C31	Ethinyl estradiol	Org 30659
635	C32	Ethinyl estradiol	Org 30659
636	C33	Ethinyl estradiol	Org 30659
637	C34	Ethinyl estradiol	Org 30659
638	C35	Ethinyl estradiol	Org 30659
639	C36	Ethinyl estradiol	Org 30659
640	C37	Ethinyl estradiol	Org 30659
641	C38	Ethinyl estradiol	Org 30659
642	C39	Ethinyl estradiol	Org 30659
643	C40	Ethinyl estradiol	Org 30659
644	C41	Ethinyl estradiol	Org 30659
645	C42	Ethinyl estradiol	Org 30659
646	C43	Ethinyl estradiol	Org 30659
647	C44	Ethinyl estradiol	Org 30659
648	C45	Ethinyl estradiol	Org 30659
649	C46	Ethinyl estradiol	Org 30659
650	C47	Ethinyl estradiol	Org 30659
651	C48	Ethinyl estradiol	Org 30659

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
652	C49	Ethinyl estradiol	Org 30659
653	C50	Ethinyl estradiol	Org 30659
654	C51	Ethinyl estradiol	Org 30659
655	C52	Ethinyl estradiol	Org 30659
656	C53	Ethinyl estradiol	Org 30659
657	C54	Ethinyl estradiol	Org 30659
658	C55	Ethinyl estradiol	Org 30659
659	C56	Ethinyl estradiol	Org 30659
660	C57	Ethinyl estradiol	Org 30659
661	C58	Ethinyl estradiol	Org 30659
662	C59	Ethinyl estradiol	Org 30659
663	C60	Ethinyl estradiol	Org 30659
664	C61	Ethinyl estradiol	Org 30659
665	C62	Ethinyl estradiol	Org 30659
666	C63	Ethinyl estradiol	Org 30659
667	C64	Ethinyl estradiol	Org 30659
668	C65	Ethinyl estradiol	Org 30659
669	C66	Ethinyl estradiol	Org 30659
670	C67	Ethinyl estradiol	Org 30659
671	C1	Ethinyl estradiol	Trimegestone
672	C2	Ethinyl estradiol	Trimegestone
673	C3	Ethinyl estradiol	Trimegestone
674	C4	Ethinyl estradiol	Trimegestone
675	C5	Ethinyl estradiol	Trimegestone
676	C6	Ethinyl estradiol	Trimegestone
677	C7	Ethinyl estradiol	Trimegestone
678	C8	Ethinyl estradiol	Trimegestone
679	C9	Ethinyl estradiol	Trimegestone
680	C10	Ethinyl estradiol	Trimegestone
681	C11	Ethinyl estradiol	Trimegestone
682	C12	Ethinyl estradiol	Trimegestone
683	C13	Ethinyl estradiol	Trimegestone

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
684	C14	Ethinyl estradiol	Trimegestone
685	C15	Ethinyl estradiol	Trimegestone
686	C16	Ethinyl estradiol	Trimegestone
687	C17	Ethinyl estradiol	Trimegestone
688	C18	Ethinyl estradiol	Trimegestone
689	C19	Ethinyl estradiol	Trimegestone
690	C20	Ethinyl estradiol	Trimegestone
691	C21	Ethinyl estradiol	Trimegestone
692	C22	Ethinyl estradiol	Trimegestone
693	C23	Ethinyl estradiol	Trimegestone
694	C24	Ethinyl estradiol	Trimegestone
695	C25	Ethinyl estradiol	Trimegestone
696	C26	Ethinyl estradiol	Trimegestone
697	C27	Ethinyl estradiol	Trimegestone
698	C28	Ethinyl estradiol	Trimegestone
699	C29	Ethinyl estradiol	Trimegestone
700	C30	Ethinyl estradiol	Trimegestone
701	C31	Ethinyl estradiol	Trimegestone
702	C32	Ethinyl estradiol	Trimegestone
703	C33	Ethinyl estradiol	Trimegestone
704	C34	Ethinyl estradiol	Trimegestone
705	C35	Ethinyl estradiol	Trimegestone
706	C36	Ethinyl estradiol	Trimegestone
707	C37	Ethinyl estradiol	Trimegestone
708	C38	Ethinyl estradiol	Trimegestone
709	C39	Ethinyl estradiol	Trimegestone
710	C40	Ethinyl estradiol	Trimegestone
711	C41	Ethinyl estradiol	Trimegestone
712	C42	Ethinyl estradiol	Trimegestone
713	C43	Ethinyl estradiol	Trimegestone
714	C44	Ethinyl estradiol	Trimegestone
715	C45	Ethinyl estradiol	Trimegestone

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
716	C46	Ethinyl estradiol	Trimegestone
717	C47	Ethinyl estradiol	Trimegestone
718	C48	Ethinyl estradiol	Trimegestone
719	C49	Ethinyl estradiol	Trimegestone
720	C50	Ethinyl estradiol	Trimegestone
721	C51	Ethinyl estradiol	Trimegestone
722	C52	Ethinyl estradiol	Trimegestone
723	C53	Ethinyl estradiol	Trimegestone
724	C54	Ethinyl estradiol	Trimegestone
725	C55	Ethinyl estradiol	Trimegestone
726	C56	Ethinyl estradiol	Trimegestone
727	C57	Ethinyl estradiol	Trimegestone
728	C58	Ethinyl estradiol	Trimegestone
729	C59	Ethinyl estradiol	Trimegestone
730	C60	Ethinyl estradiol	Trimegestone
731	C61	Ethinyl estradiol	Trimegestone
732	C62	Ethinyl estradiol	Trimegestone
733	C63	Ethinyl estradiol	Trimegestone
734	C64	Ethinyl estradiol	Trimegestone
735	C65	Ethinyl estradiol	Trimegestone
736	C66	Ethinyl estradiol	Trimegestone
737	C67	Ethinyl estradiol	Trimegestone
738	C1	Ethinyl estradiol	Dienogest
739	C2	Ethinyl estradiol	Dienogest
740	C3	Ethinyl estradiol	Dienogest
741	C4	Ethinyl estradiol	Dienogest
742	C5	Ethinyl estradiol	Dienogest
743	C6	Ethinyl estradiol	Dienogest
744	C7	Ethinyl estradiol	Dienogest
745	C8	Ethinyl estradiol	Dienogest
746	C9	Ethinyl estradiol	Dienogest
747	C10	Ethinyl estradiol	Dienogest

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
748	C11	Ethinyl estradiol	Dienogest
749	C12	Ethinyl estradiol	Dienogest
750	C13	Ethinyl estradiol	Dienogest
751	C14	Ethinyl estradiol	Dienogest
752	C15	Ethinyl estradiol	Dienogest
753	C16	Ethinyl estradiol	Dienogest
754	C17	Ethinyl estradiol	Dienogest
755	C18	Ethinyl estradiol	Dienogest
756	C19	Ethinyl estradiol	Dienogest
757	C20	Ethinyl estradiol	Dienogest
758	C21	Ethinyl estradiol	Dienogest
759	C22	Ethinyl estradiol	Dienogest
760	C23	Ethinyl estradiol	Dienogest
761	C24	Ethinyl estradiol	Dienogest
762	C25	Ethinyl estradiol	Dienogest
763	C26	Ethinyl estradiol	Dienogest
764	C27	Ethinyl estradiol	Dienogest
765	C28	Ethinyl estradiol	Dienogest
766	C29	Ethinyl estradiol	Dienogest
767	C30	Ethinyl estradiol	Dienogest
768	C31	Ethinyl estradiol	Dienogest
769	C32	Ethinyl estradiol	Dienogest
770	C33	Ethinyl estradiol	Dienogest
771	C34	Ethinyl estradiol	Dienogest
772	C35	Ethinyl estradiol	Dienogest
773	C36	Ethinyl estradiol	Dienogest
774	C37	Ethinyl estradiol	Dienogest
775	C38	Ethinyl estradiol	Dienogest
776	C39	Ethinyl estradiol	Dienogest
777	C40	Ethinyl estradiol	Dienogest
778	C41	Ethinyl estradiol	Dienogest
779	C42	Ethinyl estradiol	Dienogest

Table No. 6. Combination Examples

Example Number	COX-2 Inhibitor	Estrogen Sex Steroid	Progestin Sex Steroid
780	C43	Ethinyl estradiol	Dienogest
781	C44	Ethinyl estradiol	Dienogest
782	C45	Ethinyl estradiol	Dienogest
783	C46	Ethinyl estradiol	Dienogest
784	C47	Ethinyl estradiol	Dienogest
785	C48	Ethinyl estradiol	Dienogest
786	C49	Ethinyl estradiol	Dienogest
787	C50	Ethinyl estradiol	Dienogest
788	C51	Ethinyl estradiol	Dienogest
789	C52	Ethinyl estradiol	Dienogest
790	C53	Ethinyl estradiol	Dienogest
791	C54	Ethinyl estradiol	Dienogest
792	C55	Ethinyl estradiol	Dienogest
793	C56	Ethinyl estradiol	Dienogest
794	C57	Ethinyl estradiol	Dienogest
795	C58	Ethinyl estradiol	Dienogest
796	C59	Ethinyl estradiol	Dienogest
797	C60	Ethinyl estradiol	Dienogest
798	C61	Ethinyl estradiol	Dienogest
799	C62	Ethinyl estradiol	Dienogest
800	C63	Ethinyl estradiol	Dienogest
801	C64	Ethinyl estradiol	Dienogest
802	C65	Ethinyl estradiol	Dienogest
803	C66	Ethinyl estradiol	Dienogest
804	C67	Ethinyl estradiol	Dienogest

BIOLOGICAL ASSAYS

The utility of the combinations of the present invention can be shown by the following assays. These assays are performed in vitro and in animal models essentially using procedures recognized to show the utility of the present invention.

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test is performed with materials, reagents and procedures essentially as described by Winter, et al., (Proc. Soc. Exp. Biol. Med., 111, 544 (1962)). Male Sprague-Dawley rats are selected in each group so that the average body weight is as close as possible. Rats are fasted with free access to water for over sixteen hours prior to the test. The rats are dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline is administered and the volume of the injected foot is measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot is again measured. The average foot swelling in a group of drug-treated animals is compared with that of a group of placebo-treated animals and the percentage inhibition of edema is determined (Otterness and Bliven, Laboratory Models for Testing NSAIDS, in Non-steroidal Anti-Inflammatory Drugs, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure.

Rat Carrageenan-induced Analgesia Test

The analgesia test using rat carrageenan is performed with materials, reagents and procedures essentially as described by Hargreaves, et al., (Pain, 32, 77 (1988)). Male Sprague-Dawley rats are treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats are placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty minute period, thermal stimulation is begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell turns off the lamp and timer when light is interrupted by paw withdrawal. The time until the rat withdraws its foot is then measured. The withdrawal latency in seconds is determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal determined.

Evaluation of COX-1 and COX-2 activity in vitro

The compounds of this invention exhibit inhibition in vitro of COX-2. The COX-2 inhibition activity of the compounds of this invention illustrated in the Examples is determined by the following methods.

a. Preparation of recombinant COX baculoviruses

A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 is cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D. R. O'Reilly et al (Baculovirus

Expression Vectors: A Laboratory Manual (1992)). Recombinant baculoviruses are isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells (2x10 e8) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M. D. Summers and G. E. Smith, A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses are purified by three rounds of plaque purification and high titer (10E7-10E8 pfu/ml) stocks of virus are prepared. For large scale production, SF9 insect cells are infected in 10 liter fermentors (0.5×10^6 /ml) with the recombinant baculovirus stock such that the multiplicity of infection is 0.1. After 72 hours the cells are centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate is centrifuged at 10,000xG for 30 minutes, and the resultant supernatant is stored at -80° C. before being assayed for COX activity.

b. Assay for COX-1 and COX-2 activity

COX activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after ten

minutes at 37° C./room temperature by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE2 formed is measured by standard ELISA technology (Cayman Chemical).

The examples herein can be performed by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

The invention being thus described, it is apparent that the same can be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications and equivalents as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.